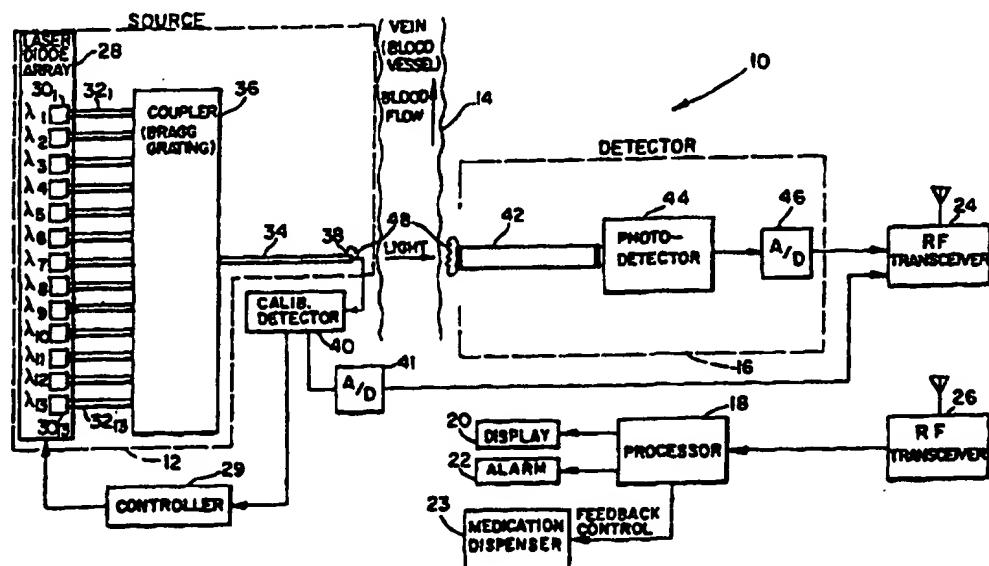




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61B 5/00		A1	(11) International Publication Number: WO 98/01071
			(43) International Publication Date: 15 January 1998 (15.01.98)
(21) International Application Number: PCT/US97/11832 (22) International Filing Date: 8 July 1997 (08.07.97) (30) Priority Data: PCT/US96/11435 8 July 1996 (08.07.96) WO (34) Countries for which the regional or international application was filed: US et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): ANIMAS CORPORATION [US/US]; Suite 217, 2460 General Armistead Avenue, Norristown, PA 19403 (US).		Published <i>With international search report.</i>	
(72) Inventor; and (75) Inventor/Applicant (for US only): CROTHALL, Katherine, D. [US/US]; 141 Maple Hill Road, Gladwyne, PA 19035 (US).			
(74) Agents: JABLON, Clark, A. et al.; Panitch Schwarze Jacobs & Nadel, P.C., 36th floor, 1601 Market Street, Philadelphia, PA 19103 (US).			

(54) Title: **IMPLANTABLE SENSOR AND SYSTEM FOR IN VIVO MEASUREMENT AND CONTROL OF FLUID CONSTITUENT LEVELS**



(57) Abstract

An in vivo implantable sensor (10) obtains spectra of body fluid constituents, and processes the spectra to determine the concentration of a constituent of the body fluid. The sensor includes an optical source (12), and detector (16). The source emits light at a plurality of different, discrete wavelengths, including at least one wavelength in the infrared region. The light interacts with the body fluid and is received at the detector. The light at the plurality of different wavelengths has a substantially collinear optical path through the fluid with respect to each other. When measuring fluid constituents in a blood vessel (14), such as blood glucose, the light at the plurality of different wavelengths is emitted in a substantially single period of time. The spectra are corrected for artefacts introduced from extraneous tissue in the optical path between the source (12) and the detector (16).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bohnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

TITLE OF THE INVENTION
IMPLANTABLE SENSOR AND SYSTEM FOR IN VIVO
MEASUREMENT AND CONTROL OF FLUID CONSTITUENT LEVELS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application is a continuation-in-part of copending International Application No. PCT/US96/11435 filed July 8, 1996, entitled "IMPLANTABLE SENSOR AND SYSTEM FOR MEASUREMENT AND CONTROL OF BLOOD CONSTITUENT LEVELS" and which designated the United States.

BACKGROUND OF THE INVENTION

10 The present invention relates generally to medical apparatus and methods for determining in vivo the concentration of a chemical constituent in a body fluid using direct spectroscopic analysis of the fluid, and for removing or obviating actual or potential artifacts from measured spectral data.

15 In medicine, the measurement of the composition of blood and other body fluids is an often invaluable diagnostic tool and is used as a basis for the titration of medicines and the determination of therapy. Broadly speaking, there are two classes of devices used for the measurement of chemical constituents; chemical and optical. The chemical techniques are the most wide-spread and essentially all techniques used in the clinical laboratory are based on chemical techniques. Chemical techniques invariably rely upon the constituent reacting with a "reagent" and either an optical or electrical measurement of the reagent or the by-products of the reaction. 20 Unfortunately, the present chemical techniques have many drawbacks, including the following drawbacks:

25 (1) Present commercially available instruments are invasive and require, generally, a drop of fluid to determine the chemical constituents.

(2) Present commercial instruments require a unique chemical reagent for the determination of each constituent. The reagents are generally expendable and need to be replaced, frequently after each measurement. Instrument maintenance is thus expensive and inconvenient, particularly for an implantable device.

5 (3) Implantable chemical sensors suffer from drift due to lack of stability of the reagents at body temperature over a period of time, and short lifetime due to biocompatibility problems.

(4) Chemical sensors generally consume the constituent they are to measure, affecting accuracy. In an implantable sensor, tissue reaction with the sensor invariably diminishes the supply of the constituents, causing a reduction in accuracy.

10

Optical techniques have been hailed by researchers as a means to overcome all the problems associated with chemical techniques, as they do not utilize a reagent or require any sort of chemical reaction and they do not require direct interaction of the sensor with the chemical constituent. Optical techniques can theoretically provide continuous, non-invasive, simultaneous determination of multiple chemical constituents. Despite the promise of optical techniques and the efforts by numerous groups throughout the world to perfect such techniques, optical techniques are rarely used in clinical medicine. The pulse oximeter and an instrument which measures percent of body fat are notable exceptions.

20 One sensor particularly sought by researchers has been a home use glucose sensor for insulin-dependent diabetics. Ideally, such a sensor would be non-invasive or permanently implantable, would provide a continuous or quasi-continuous means of measurement of blood glucose, and would be accurate over the physiological range of blood chemistry and other conditions and would require minimal patient intervention. There are reportedly over 60 groups throughout the world who are currently attempting to develop such a sensor, yet no group is known to be close to success. The rationale behind these efforts are the staggering cost of the complication of diabetes on both the patient and the health care system. Studies have shown that the complications of diabetes can be reduced significantly with tight control of blood sugar.

25

5

Diabetes is a major chronic disease, costing the United States between \$ 90 and \$ 110 billion annually in health care costs alone. Approximately 750,000 people in United States have insulin dependent diabetes mellitus (IDDM), also known as Type I, Juvenile onset, or ketosis prone diabetes. Another 16 million people have non-insulin dependent diabetes mellitus (NIDDM), also known as Type II or adult onset diabetes. Globally, the World Health Organization estimates the number of diabetics to exceed 80 million, many of whom are undiagnosed.

10

Acute complications from diabetes involve metabolic abnormalities such as hypoglycemia and ketoacidosis. Long term complications involve the blood vessels and tissues leading to retinopathy, stroke, myocardial infarction, heart failure, arterial occlusive diseases, nephropathy, kidney failure, and peripheral neuropathy. For example, diabetes produced blindness in over 39,000 people within the United States last year. About 25% of people with IDDM and 10% of the people with NIDDM have proliferative retinopathy within 15 years after diagnosis of diabetes. About 34% of 15 IDDM and 19% of NIDDM have diabetic kidney disease within 15 years of diagnosis. Although all these diseases occur in the general population, they occur early and far more frequently, and progress more rapidly in diabetics.

20

There have been several studies which have proven that the occurrence or progression of complications of diabetes can be reduced substantially in IDDM diabetics if their blood sugars can be maintained at near normal levels. The Diabetes Control and Complications Trial (DCCT) was a nine year randomized prospective study involving more than 1,400 subjects. The DCCT compared the complication rate following standard IDDM management (mean glucose 195 mg/dl) versus tight control with frequent fingerstick blood testing and frequent insulin injections (mean glucose levels 155 mg/dl). Intensive therapy was shown to reduce the risk for development of retinopathy by 76% and reduce the progression of retinopathy by 54%. A smaller scale study known as the Oslo study followed 45 insulin dependent diabetics, randomized into three groups: multiple insulin injections, continuous subcutaneous insulin infusion (CSII), and conventional twice daily insulin injections. Near 25

normoglycemia was obtained with CSII and multiple injections, but not with conventional therapy. After two years, the CSII and multiple injections groups showed little deterioration as measured by the number of microaneurisms and hemorrhages whereas the conventional therapy group showed significant deterioration.

5

Several observations can be made regarding these studies:

Although tight control reduces the secondary complication rate of diabetes significantly compared to loosely controlled diabetes, the risk of these complications is still several times higher than with the non-diabetic population.

10

Tight control involves a significant amount of inconvenience and pain, rendering such compliance an elusive goal for many, if not most diabetics. For example, to determine the appropriate insulin injection, a diabetic must measure his blood glucose at least five to six times daily which involves pricking one's fingers to draw blood and then measuring for blood glucose with a glucometer. For many patients, the drawing of blood is painful and inconvenient, in fact substantially more painful and inconvenient than the insulin injection.

15

Both studies pointed to a significant (two to three times) increase in severe and at times symptomless hypoglycemia for patients under tight control versus those under conventional therapy. Severe hypoglycemia leads to loss of consciousness and at times even coma. In patients under tight control, the incidence of severe hypoglycemia ran 0.6 to 0.8 incidents per year whereas for patients under conventional therapy, the incidence ran 0.2 to 0.4 incidents per year. For this reason, a continuous or quasi-continuous sensor which can provide an alarm is desired.

20

The blood glucose levels with patients under a tight control regime has a mean value of 155 mg/dl and varies from a low of 120 mg/dl to a high of 190 mg/dl over the course of a day. These levels are still quite a bit higher than the glycemia of non-diabetics which have a mean glycemia of 110 mg/dl and a variance from 90 to 120 mg/dl over the course of a day. Although the DCCT indicates the desirability of even a further reduction of blood glucose, the risk of hypoglycemia mitigates against any further reduction.

5

It is believed that a system which can maintain blood sugars to true normal levels (90-120 mg/dl) could potentially eliminate the complications of diabetes. Such a system would have an insulin infusion pump and a glucose sensor. Neither pump nor sensor would require much interaction on the part of the patient and would certainly be painless. The pumps are already well developed. The missing link is a sensor which can continuously measure blood sugar, is either non-invasive or implantable, and is accurate over a large range of physiological ranges.

10

The approaches taken by researchers to measure blood glucose consist of a variety of techniques, both optical and chemical. A variety of researchers have attempted implantable chemical sensors, but these sensor seem to invariably fail for the reasons outlined above. U.S. Patent No. 5,353,792 (Lubbers et al.) discloses a variation on the chemical sensor which uses "optically excitable and readable indicating substances", one of which could presumably interact with glucose. The drawback to this approach is the same as other chemical techniques, namely the substances need to presumably interact directly with the constituent to be measured and therefore can potentially be depleted with time, or alternatively, the substances become blocked from interaction with the constituent due to encapsulation tissue. Another variation to the Lubbers et al. approach are affinity sensors based on fiber optics, described in Schultz, J.S. et al., "Affinity Sensor: A New Technique for Developing Implantable Sensors for Glucose and Other Metabolites," Diabetes Care, Vol. 5, No. 3, pp. 243, May-June 1982; and Mansouri, S. et al., Bio/technology, Vol. 2, pp. 385, 1984. These sensors also suffer from long term reduction in sensitivity.

15

The optical techniques also include a variety of approaches. Most of the approaches attempted have been non-invasive, transcutaneous means utilizing infrared spectroscopy. Infrared spectroscopy is based on the absorption of infrared light. The amount of absorption is dependent upon the concentration and light pathlength through the fluid being measured. Each chemical constituent has its own unique absorption spectra, depending upon the weight of each atom and strength of each molecular bond in a molecule. In theory, given enough signal to noise, one should be able to

20

determine precisely the presence and concentration of each chemical constituent in a fluid, such as blood. Transcutaneous infrared spectroscopic techniques suffer from variability in optical coupling, poor signal to noise, and excessive artifacts. No device utilizing such techniques has yet been shown to work reliably. One technique disclosed in U.S. Patent Application No. 08/500,388, filed July 6, 1995, entitled "IMPLANTABLE SENSOR AND SYSTEM FOR MEASUREMENT AND CONTROL OF BLOOD CONSTITUENT LEVELS," partially solved the coupling and signal to noise problem by implanting the sensor, as opposed to using it transcutaneously. A more detailed analysis of these two approaches is discussed below.

Several other optical approaches have also been attempted. U.S. Patent No. 4,704,029 (Van Heuvelen) discloses an implantable device in which the concentration of glucose is inferred by a measurement of the refractive index of blood by an optical device in direct contact with blood. This device has many drawbacks, including the need for the device to have direct contact with blood. U.S. Patent No. 5,209,231 (Cote et al.) discloses a somewhat different approach which is to measure the rotation of a plane of polarized light through blood or another body fluid. This technique and others like it use a very small rotation (millidegrees) and hence produce a very small signal, making the method very sensitive to scattering, movement, and pathlength variability.

As mentioned earlier, although in theory, given enough signal to noise, one should be able to determine the concentration of the constituents through infrared spectroscopy, in practice, such determinations have been shown to be very challenging. Measurement of glucose, in particular has been shown to be very difficult, even on an in vitro basis. The reasons are several fold:

(1) The body tissue and blood in particular are primarily composed of water. Water has a very strong intrinsic absorption in the infrared (IR) region, particularly in the mid IR region. The strong absorption by water severely reduces the signal to noise ratio, unless pathlengths are kept quite small. In the mid and near IR regions, pathlengths

must be down to approximately 25 um or 1000 um, respectively, to obtain an acceptable signal to noise ratio.

(2) The concentrations of the constituents are low compared to that of water. The spectra of the various constituents in blood and other body fluids tend to overlap with one another and that of water, and almost all of the concentrations of constituents vary over the physiological range. For example, in the measurement of blood glucose concentration, the measurement must be taken against a backdrop wherein the concentration of the other constituents is constantly changing and the spectra of the other constituents overlap that of glucose.

(3) In the near IR region, both positions of the peaks and intensity of the water spectra shift with temperature and pH, further complicating the measurement.

(4) Blood and other body tissues tend to scatter light substantially, further reducing the signal to noise ratio detected by a sensor and further adding variability.

Despite these difficulties, several researchers have been able to determine glucose and other constituent concentration with acceptable or near acceptable accuracy on an in vitro basis, using multivariate techniques for the analysis of the spectra. It should be emphasized that these measurements were done on an in vitro basis, with a state-of-the art spectrophotometer, with a well-optimized set-up, and generally with factors not possible to reproduce on an in vivo basis, (i.e., temperature stability, constant pathlength). In addition, these measurement typically required a large number of spectral points (> 100) to obtain good accurate predictions of the constituent concentration. Hence, to make these measurements on an in vivo basis, extraordinary measures must be taken to ensure that the signal to noise ratio is the same or better as the in vitro measurements, and that there are now added additional artifacts.

Given the difficulty with in vitro measurements, it should come as no surprise that the transcutaneous means have not worked. In a transcutaneous sensor, the light "sees" a far large number of variables then what is seen on an in vitro basis due to the interaction of light with skin, fat, bone, and the like. Sorting out the spectra becomes very difficult. In addition, the signal to noise ratio obtainable with such a

5

means is significantly lower than in vitro measurements due to substantially poorer optical coupling, the presence of additional scattering tissues (e.g., skin), and absorption by tissue which may not contain glucose (e.g., fat). Finally, given the accuracy necessary in the spectra to obtain an accurate determination of the constituent concentration, excessive artifacts are apt to obscure such measurements.

10

15

20

25

Attempts were made to eliminate some of the problems related to transcutaneous infrared sensor by using an implantable blood glucose sensor described in U.S. Patent Application No. 08/500,388, filed July 6, 1995, entitled "IMPLANTABLE SENSOR AND SYSTEM FOR MEASUREMENT AND CONTROL OF BLOOD CONSTITUENT LEVELS". For example, this sensor improved the signal to noise ratio by implanting the sensor, thereby eliminating some of the sources of optical loss. The sensor in this patent application consists of spatially separated pairs of infrared light sources and infrared sensitive detectors. Each source and detector pair is spaced so that light from the source passes through a blood vessel and is received by the detector. Each source outputs a different discrete narrow band of light. The significant spatial separation between each source/detector pair causes a significant spatial separation of the spectral lines output by the sources. Each detector thus "sees" a different spatial region of the blood vessel. Due to this fact and the dynamic nature of blood vessels, it is believed that the spectral information output from the detectors cannot be used to obtain sufficiently accurate blood glucose levels.

Furthermore, the measurement technique in the above-described patent application fails to correct for spectral artifacts due to scattering and absorption by the blood vessel wall and any other tissue that may be in the optical path between the output of each source and the input of the corresponding detector. In addition, the diameter of a blood vessel is neither constant over time, since a blood vessel bulges and collapses with each heartbeat, nor uniform in diameter. In addition, blood is not spatially homogeneous, so there can be significant variability in scattering from point to point. Pathlength variability in the measurement techniques described in the above-identified patent application may thus be on the order of 1 part in 100 (in absorbtivity

units), which is large enough to destroy the usefulness of the spectral information obtained therefrom.

Many of the problems discussed above also arise when measuring other body fluid constituents. In sum, there are considerable obstacles to obtaining accurate in vivo measurements of body fluid constituents. Despite a long-felt need, sensors and spectral analysis techniques heretofore have been inadequate for this task. The present invention fulfills such a need and provides both sensors and spectral analysis techniques which yield accurate in vivo measurements of body fluid constituents.

BRIEF SUMMARY OF THE INVENTION

The present invention provides methods and apparatus for determining concentration of constituents of body fluids in a mammal using in vivo spectroscopy. A sensor system is implanted in the mammal. The sensor system includes a source of light which emits at a plurality of different wavelengths and a detector for detecting light emitted from the source. At least one of the wavelengths is in the infrared region. The source and the detector are arranged so that the light output from the source interacts with a body fluid before being received by the detector, and so that the light from light from the plurality of different wavelengths has a substantially collinear optical path through the fluid with respect to one another. A signal is obtained at the output of the detector which contains spectra of the body fluid at each of the plurality of different wavelengths. A processor analyzes the signal to determine the concentration of at least one constituent of the body fluid.

The sensor may be disposed extravascularly to measure concentration of blood constituents. Alternatively, the sensor may be disposed within interstitial fluid or gel to measure concentration of a constituent of the interstitial fluid or gel, or the sensor may be disposed around a vascular membrane to measure concentration of a constituent of blood in the membrane.

In another embodiment of the invention, a medication dispenser is connected to the sensor for dispensing doses of medicine in response to the concentration of the chemical constituent output from the processor.

5 To minimize artifacts when measuring fluid constituents in a blood vessel such as a vein, light from the plurality of different wavelengths is emitted in a substantially single period of time and the spectra is corrected for extraneous tissue in the optical path between the source and the detector.

BRIEF DESCRIPTION OF THE DRAWINGS

10 The following detailed description of preferred embodiments of the invention will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there is shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities shown. In the drawings:

15 Fig. 1 is a schematic diagram of an in vivo sensor in accordance with one preferred embodiment of the present invention;

Fig. 2 is a schematic diagram of a source which may be used in the sensor of Fig. 1;

20 Fig. 3A is a sectional view of a first physical implementation of a device for mounting implantable portions of the sensor of Fig. 1 thereon, as the device appears attached to a vein;

Fig. 3B is a side elevational view of the device of Fig. 3A;

25 Fig. 3C is a sectional view of a second physical implementation of a device for mounting implantable portions of the sensor of Fig. 1 thereon, as the device appears attached to a vein;

Fig. 4A is a sectional view of a third physical implementation of a device for mounting implantable portions of the sensor of Fig. 1 thereon, as the device appears attached to a vascular membrane;

Fig. 4B is a side elevational view of the device of Fig. 4A;

Fig. 4C is a sectional view of a fourth physical implementation of a device for mounting implantable portions of the sensor of Fig. 1 thereon, as the device appears attached to a vascular membrane;

5 Fig. 5 is a schematic diagram of source having a single output which may be used in the sensor of Fig. 1;

Fig. 6 is a schematic diagram of another single output source which may be used in the sensor of Fig. 1;

10 Fig. 7 is a schematic diagram of an alternative source and detector arrangement for use in the sensor of Fig. 1;

Figs. 8 and 9 are schematic diagrams of in vivo sensors in accordance with additional embodiments of the present invention which are particularly useful for measuring within interstitial fluid or gel; and

15 Fig. 10 is a flowchart of the steps for processing spectra obtained from an in vivo sensor of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery that the concentration of a chemical constituent of body fluid may be accurately detected in vivo by directing electromagnetic radiation or light energy (hereafter, "light") containing a plurality of different infrared wavelengths, and particularly, near-infrared wavelengths, through the body fluid so that the light of the plurality of different wavelengths forms a substantially collinear path with respect to each other as they pass through the fluid. It has been further discovered that the concentration of glucose is one chemical constituent of body fluid that may be accurately detected in this manner, and that the glucose level may be measured within a blood vessel (e.g., vein), within a vascular membrane, or within interstitial fluid or gel (hereafter, "interstitial fluid"). It was further discovered that to obtain accurate concentrations of chemical constituents of body fluids, such as glucose, in rapidly changing anatomical structures such as veins or

necessary to emit and detect all of the different wavelengths of light in a substantially single period of time.

5 Fig. 1 is a schematic block diagram of an implantable sensor system 10 for analyzing chemical constituents of body fluids in a mammal, in accordance with a first embodiment of the present invention. This embodiment detects the concentration of a chemical constituent in blood flowing through a vein, and is particularly useful for detecting the concentration of blood glucose levels. The physical structure of one embodiment of the sensor system 10 is shown in Figs. 3A-3C, discussed below. The components shown in the figures are not to scale.

10 Referring to Fig. 1, the sensor system 10 includes (i) a light source 12 for emitting at a plurality of different infrared wavelengths into vein 14, (ii) a detector 16 for detecting light emitted by the light source 12 and which has interacted with the blood in the vein 14 and outputting a signal which contains spectral information of blood constituents, and (iii) a processor 18 for analyzing the spectral information contained therein, and determining the concentration of at least one chemical constituent in the blood from the spectral information. A display 20 and an alarm 22 are connected to the processor 18 for receiving display data and alarm conditions from the processor 18 based on the determined concentration. The output of the processor 18 may optionally be used for feedback control, such as to automatically control a medication dispenser 23. One type of medication dispenser 23 may be an externally mounted or internally implanted insulin infusion pump.

15

20 The light source 12 and detector 16 are positioned extravascular and are arranged opposite to, and facing each other, and so that the output of the light source 12 goes through approximately the center of the vein 14. The output of the light source 12 and the input of the detector 16 are in close proximity to, or in contact with, the outer wall of the vein 14, as described in more detail with respect to Fig. 2. In one 25 suitable embodiment of the invention wherein the diameter of the vein 14 is between 0.3-1.0 mm, the distance between the output of the light source 12 and the vein wall,

and the distance between the input of the detector 16 and the vein wall is less than 100 μm (0.1 mm).

Depending on the needs of the patient and the sophistication and miniaturization of the system components, some or all of the components of the sensor system 10 are implanted. In Fig. 1, the light source 12 and the detector 16 are implanted in the person, and the processor 18 is external to the person. For example, the processor 18 may be worn on a person's wrist or belt. The implanted components communicate with the external components via suitable telemetry circuitry, such as a pair of RF transceivers 24 and 26 associated with the implanted and non-implanted components, respectively. Alternatively, the processor 18 may be implanted and connected directly to the output of the detector 16, and the display 20 and alarm 22 may be external to the person. In this configuration, the processor 18 may communicate with the display 20 and alarm 22 via RF transceivers connected respectively to the output of the processor 18 and the inputs of the display 20 and alarm 22. If the output of the processor 18 is used for feedback control, the medication dispenser 23 may be either external or internal to the person.

An important feature of the invention is the light source 12 which outputs light at a plurality of different infrared wavelengths, wherein the light from the wavelengths have a substantially collinear optical path with respect to one another. Collinearity is important because the sensor 10 must detect relative differences in absorptivity of the order of one part in 10^4 from one wavelength to the next in order to measure relatively dilute substances in a body fluid, such as glucose in blood. If the optical paths are not substantially collinear, variations in scattering, absorption, or pathlength differences may obscure the desired spectral information.

Fig. 1 shows one preferred light source 12 for producing such an output which is particularly useful in measuring concentrations of blood glucose.

The light source 12 contains a light emitting device 28 in the form of a laser diode array which has a plurality of individual laser diodes, such as thirteen

individual laser diodes 30_1 - 30_{13} . Each laser diode 30 produces a discrete wavelength λ_1 - λ_{13} . At times, it may be necessary to spectrally filter the output of one of the diodes 30 to obtain a more spectrally pure output. The state of the light emitting device 28, including the state of the individual laser diodes 30_1 - 30_{13} is controlled by a controller 29. The output of each laser diode 30 is coupled to an input of a respective single-mode optical fiber 32_1 - 32_{13} , having a core diameter of about 9 μm . The output of the respective optical fibers 32_1 - 32_{13} are coupled to an input of one single-mode optical fiber 34 of a similar construction and core diameter as the optical fibers 32, via a Bragg diffraction grating coupler 36 or a wavelength division multiplexer/demultiplexer. At the output of the coupler 36, light from all of the individual wavelengths is substantially collinear. This coupling technique thus ensures that light at each wavelength has the identical optical path as that of every other wavelength.

The output of the one optical fiber 34, labeled as 38, is the output of the light source 12. A portion of the output of the one optical fiber 34 is diverted to a calibration detector 40 via a beam splitter (not shown) for use by the processor 18 in calibrating the output of the laser diodes 30_1 - 30_{13} . The output of the calibration detector 40 is then fed into a preamplifier (not shown) an analog-to-digital (A/D) converter 41, and finally to the RF transceiver 24. Optionally, the output of the calibration detector 40 may also be connected to the controller 29 for adjusting the power output of the light emitting device 28 (in Fig. 1, the laser diode array) to produce constant output power from pulse to pulse. One suitable calibration detector is an InGaAs detector with a two stage preamplifier. A simple temperature measuring device may at times be used to gauge the output of each of the diodes 30_1 - 30_{13} , instead of the calibration detector 40.

For detecting the concentration of glucose in blood to an accuracy of ± 18 mg/dl over the physiological range of temperature, pH and blood chemistry, it is sufficient to use about thirteen different wavelengths, wherein two wavelengths (or

5

more) are used to normalize pathlength variations, one wavelength is used for baseline offset, and the remaining ten wavelengths are used for the glucose measurement. With an accurate measurement of the temperature of the body fluid, it might be possible to reduce the number of wavelengths. Ideally, the two wavelengths chosen for pathlength normalization are not affected by "extraneous" tissue surrounding the fluid desired to be measured (in this case, blood). That is, the difference in absorptivity between the two wavelengths is not affected by "extraneous" tissue. One set of wavelengths (in nanometers) suitable for detecting the concentration of glucose in blood when the blood pathlength is 0.5 mm or less are as follows:

10

1300, 2259, 1964, 2038, 1970, 1839, 2146, 1376, 2084, 1391, 2186, 1434, 2154 nm

The first wavelength (1300) is used for baseline offset and the next two wavelengths (2259 and 1964) are used for pathlength normalization.

15

If longer pathlengths are used, the optimum wavelengths shift somewhat towards shorter wavelengths. Alternatively, wavelengths further into the infrared region or into the visible region may be useful for detecting other chemical constituents. Thus, there may be some wavelengths which are not in the infrared region. The specific number and value of wavelengths depends upon the constituent of interest and the desired accuracy of the concentration. In general, however, it is preferable to avoid spectral regions of high water absorption. Accordingly, the near-infrared region is generally preferred over the middle infrared region.

20

The particular wavelengths and spectral regions chosen are determined on a reiterative, semi-trial and error basis in conjunction with the determination of an in vitro algorithm (discussed below), taking into consideration the absorption peaks of the constituents of interest, water absorption, hardware considerations, and other consideration such as other possibly interfering tissues. In the case of the glucose sensor, the region between 900 nm and 2,500 nm was chosen, since wavelengths above 2,500 nm suffered from excessive water absorption and device limitations, and

wavelengths below 900 nm suffered from excessively weak absorption. With this in mind, blood samples from over 450 people were taken and an FT-IR spectra between 900 nm and 2,500 nm was taken on each of these samples.

5 There are a number of well-known techniques to obtain correlation of the spectra and the measured constituent values, including the Norris Regression Algorithm, Partial Least Squares, Principal Component Regression, and Neural Networks. Various of these techniques were attempted on the blood samples of 450 people on a semi-trial and error basis to achieve the following goals:

10 1. Obtain the best cross-validation, calibration, and predictive standard errors.

2. Use as few wavelengths as possible.

3. Use as short wavelengths as possible.

15 Each of these algorithms ultimately yield the choice of wavelengths and the corresponding algorithm which correlates the measured spectra to the constituent concentration. The section below entitled: "DETERMINATION OF THE IN VITRO ALGORITHM" discusses the optimization of this algorithm using the Norris Regression, which is the preferred embodiment of the invention.

20 For measuring the concentration of glucose in blood in the preferred embodiment, each laser diode 30 should output sufficient power to deliver at least 1 mW to the photodetector 44. Typically, this implies that the source output should be at least 10 mW at about 2,200 nm.

25 The detector 16 includes a collection optical fiber 42 located on the other side of the vein 14, diametrically opposite the output of the light source 12, to collect the light emitted from the light source 12 after it has traversed the vein 14. The collection optical fiber 42 has a larger core diameter than the light source output fiber 34, optimally from about 0.2 to about 1.0 mm, depending upon the size of the vein used for measurement and whether or not the vein is compressed by the sensor 10. The collection optical fiber 42 must be chosen to have good collection properties.

Thus, it should ideally have a numerical aperture (NA) of 0.39 or larger when measuring a highly scattering fluid such as blood. A large diameter core is also preferable for the collection optical fiber 42 in terms of collection efficiency and hence signal to noise. However, a fiber that is too large may cause non-linearities due to pathlength differences (through the vein) of the light collected by different areas over the aperture of the collection optical fiber 42 or photodetector 44 (discussed below). The output of the collection optical fiber 42 is fed into a photodetector 44, such as an uncooled InGaAs detector with a two stage linear preamplifier. The photodetector 44 and the preamplifier should have (1) a high degree of linearity, (2) a high signal to noise ratio, and (3) a sufficiently wide spectral bandwidth to detect the entire spectral band of the source 12. To accurately measure glucose absorptivity, the optical power readings taken by the photodetector 44 must be 10^5 greater than the noise level, and therefore the photodetector 44 must be linear over 5 decades. When using infrared wavelengths, a 5 decade requirement leaves very little room between the noise threshold on one hand and the level of linearity on the other hand. No spectral filter is required in front of the photodetector 44 unless the photodetector can detect wavelengths longer than 3,000 nanometers, where black body radiation becomes significant. In the preferred embodiment of the invention, a electronic bandpass filter (not shown) is used to limit 1/f noise and high-frequency noise. The electronic bandpass filter will typically cut-out at a frequency from about $1/2T$ to about $2/T$, where T is the pulse width of any laser diode pulse. The photodetector 44 is preferably a single element device which is sensitive over the entire range of received infrared wavelengths.

The output of the photodetector 44 is sent to an A/D converter 46, and the digitized output signal is transmitted by the RF transceiver 24, received by the external RF transceiver 26 and sent to the external processor 18. The RF transceivers 24 and 26 preferably have a range from about one to about three meters. Alternatively, the transceivers 24 and 26 may be replaced by infrared transceivers.

5

In some cases, no collection optical fiber 42 is necessary. Instead, the photodetector 44 may directly detect the light after it has passed through the vein 14. One advantage of using a collection optical fiber to receive the light is that it is relatively light in weight and small in size compared to the photodetector 44, and therefore may be less likely to cause the vein to become non-patent. A collection optical fiber also may be less prone to build-up of encapsulation tissue than a photodetector 44 since it is easier to mechanically secure an optical fiber than a photodetector with respect to a vein, and hence avoid chafing.

10

The output of the calibration detector 40, after being amplified and digitized, is connected to the RF transceiver 24 for transmission to the processor 18. The processor 18 thus receives a signal from the calibration detector 40, as well as from the collection detector 16. The processor 18 uses the measured power of both signals to make certain corrections, as discussed below.

15

20

25

Whenever a foreign object is implanted in a living body, tissue tends to build up on the object, even when the object is made of a biocompatible material. This tissue is known as "encapsulation tissue." Encapsulation tissue usually builds up over time to a certain amount and then stops growing and reaches a steady state, typically within 4-6 weeks. In Fig. 1, encapsulation tissue 48 is shown on the output 38 of the optical fiber 34 and on the input of the collection optical fiber 42. In the preferred embodiment of the invention, the optical fibers 32 and 34 may be encased in a hermetic and biocompatible jacket, with an infrared window such as sapphire at the exposed ends. The jacket and window may be coated with a hydrogel or similar material to minimize growth of encapsulation tissue. The jacket may be constructed of titanium or stainless steel or another hermetic and biocompatible material. While such measures are helpful to minimize rejection and the growth of encapsulation tissue, such tissue may likely form on exposed surfaces and must be accounted for when analyzing spectral information.

When taking measurements in rapidly moving anatomical structures such as pulsating veins, it was also discovered that to obtain an accurate measurement, the spectra must be taken at a "substantially single period of time" (i.e., the spectra must be substantially temporally coincident). This requires that the plurality of diodes at different wavelengths be pulsed within a "substantially single period of time". In particular, the spectra should be taken in a time short enough so that signal due to pathlength variations over the measurement time is much smaller than the anticipated signal of the fluid constituent. Experimental data shows that the "substantially single period of time" in veins and the like should be less than about 100 μ sec for the measurement of blood glucose. Thus, as defined herein, a "substantially single period of time" does not mean simultaneous, but rather means a time period short enough to be substantially simultaneous with respect to changes that are occurring to the fluid constituent in the measured space. For measurements taken in anatomical structures which do not experience rapid change, such as interstitial fluid or gel, longer time periods are acceptable.

In operation, each diode 30 of the laser diode array is pulsed sequentially for a fixed period time, with an off period between the different diode pulses. In one embodiment of the invention suitable for measuring the glucose concentration in blood, a pathlength change of about 10% over one second may be expected in certain veins as the vein pulsates due to blood flow. A glucose concentration of 100 mg/dl contributes in a 0.5 mm pathlength of blood an absorption of the order of 0.7×10^{-4} at 2,273 nm, one of the strongest glucose bands in the near-infrared range. If two consecutive wavelength measurements having an accuracy of one part in 10^5 is desired, the measurements must be taken within 0.1 milliseconds of one another to obtain a temporally coincident measurement. That is, the entire spectra must be taken within 0.1 milliseconds. In one embodiment of the invention which meets this criterion, each diode 30 is pulsed sequentially for about 3 μ sec, with an off period of about 3 μ sec between the different diode pulses. Thus, a thirteen wavelength

embodiment requires about 75 μ sec (0.075 milliseconds) for a complete cycle of pulses. The diode pulsing is controlled by the controller 29.

5 To further minimize temporal artifacts, diode pairs 30 which are very close together in wavelength or which are used for pathlength calibration should be pulsed in sequence one after the other. For the sample wavelengths listed above, the diodes 30 at pathlength calibration-related wavelengths 1,964 nm and 2,259 nm are pulsed next to one another, as are the diodes 30 at close wavelength pairs 1,964 nm and 1,970 nm, and 2,154 and 2,146 nm.

10 To improve the signal to noise ratio, it is acceptable to take a number of repeated spectra N, over a relatively short period of time. The time period should be short enough so that there is no appreciable change in the constituent concentration. For a glucose sensor, this period of time might be several minutes. The processor 18 would then either average the N spectra, or would compute the constituent 15 concentration and then average the N predicted values of constituent(s). Such a scheme provides a square-root N improvement in signal to noise. If there are changes in pathlength, pH, or temperature, over the N samples, it is generally preferable to average the predicted concentration of the constituents as opposed to averaging the spectra and then predicting the concentrations.

20 In Fig. 1 (and Figs. 3C, 4C, and 5-7 discussed below), the optical fibers 34 and 42 function as a light delivery system for the active elements of the source 12 and the detector 16, and also provide flexibility in arranging the sensor components within its housing. Likewise, in Fig. 2, the optical fiber 54 provides a similar function 25 for delivering light. If other means are used to adequately optically mix the light from the plurality of different source wavelengths, one or all of the optical fibers 34, 42 and 54 may be eliminated and light may be directly emitted or received by the active respective sensor components. For example, the output of the coupler 36 may be directly emitted into the vein 14, and the photodetector 44 may be arranged to directly receive emitted light which passes through the vein 14. Nonetheless, the preferred

embodiment of the invention uses optical fibers to deliver the light to active sensor components.

Fig. 2 shows an alternative embodiment of a light source 12'. In this embodiment, the light output from the laser diode array become collinear by mixing of the beams in a long optical fiber. Specifically, the outputs of the individual laser diodes 30₁-30₁₃ are fed into individual multimode optical fibers 50₁-50₁₃. One suitable multimode fiber 50 has a core diameter of about 100 μm , and forms a fiber bundle 52 having a diameter of about 0.5 mm. The output of the multimode fiber bundle 52 is fed into the input of a single core multimode optical fiber 54 of approximately the same diameter as the fiber bundle 52. The single core multimode fiber 54 has a significant length, such as a length greater than 1 meter, to allow substantial wavelength mixing to occur as the light beams travel toward the output. (Although reference is made to "wavelength mixing", the individual diodes are pulsed sequentially and not simultaneously.) To minimize the space required by the long optical fiber 54, the fiber 54 may be coiled in tight loops.

Referring to Fig. 1, the single-mode optical fiber 34 need not have any significant length because the wavelength mixing occurs in the coupler 36, and thus the light of the plurality of wavelengths are already mixed at the input of the optical fiber 34. The detector used for the embodiment of Fig. 2 is not shown, but it should have a similar diameter as the optical fiber 54.

Fig. 3A shows a sectional view of a first embodiment of a ring-like device 60 for mounting implantable portions of the sensor system 10 thereon and for maintaining a fixed relationship between the output of the light source 12 and the input of the detector 16. Fig. 3B shows a side elevational view of the sensor of Fig. 3A. Both the source 12 and the detector 16 are hidden from view in Fig. 3B. The source 12 is shown in phantom in Fig. 3B. Referring to Figs. 3A and 3B, the vein 14 extends through the center of the device 60. The device 60 is preferably constructed of titanium or another suitable biocompatible material. The light source 12 and the

detector 16 are mounted in a pocket of the device 60, and their respective outputs and inputs are protected by windows 62 and 64 of biocompatible and infrared transmissive material, such as sapphire. The windows 62 and 64 and ring-portion of the device 60 may be coated with a hydrogel or another polymer to minimize growth of encapsulation tissue. To further inhibit the growth of encapsulation tissue, the device 60 should be designed to minimize sharp edges. The device 60 may be constructed in two C-shaped halves which are connected together at joints 66 and 68 after placement around the vein 14.

As discussed above, the source light may be directly emitted into the vein 14, and directly detected by respective active sensor components, or optical fibers may be used as a light delivery system for the active elements of the source 12 and the detector 16. Fig. 3A shows the direct emission implementation. Fig. 3C shows a second embodiment of a mounting device 82 which uses the light delivery system implementation wherein the output and input ends of the optical fibers 34 and 42, respectively, are mounted to the device 82. In the light delivery system implementation, the active components of the device 82, including the light emitting source 28 and photodetector 44, are located remotely from the device 82.

The sensor 10 may also be used to measure concentration of a constituent of fluid in a vascular membrane, such as the peritoneal membrane. Fig. 4A shows a sectional view of a third embodiment of a direct emission device 84 for use with a vascular membrane 86. Fig. 4B shows a side elevational view of the sensor of Fig. 4A. Referring to Figs. 4A and 4B, the device 84 is generally U-shaped as oriented in Fig. 4A (C-shaped if rotated 90 degrees to the left or right), and thus defines a slot 88. The vascular membrane 86 is disposed in the slot 88. Implantable portions of the sensor system 10 are mounted in pockets of the device 84 on either sides of the slot 88. The device 84 thus maintains a fixed relationship between the output of the light source 12 and the input of the detector 16. The device 84 may include the same coatings and windows 62 and 64, and may be constructed of the same

5

materials, as the device 60 of Fig. 3A. Unlike the device 60 which requires a two piece housing portion, the housing portion of the device 84 may optionally be constructed from a single unitary piece of U-shaped material. Fig. 4C shows a fourth embodiment of a device 90 for use with a vascular membrane 86 which uses the light delivery system implementation, wherein the output and input ends of the optical fibers 34 and 42, respectively, are mounted to the device 90.

10

Referring to Figs. 1 and 2, the light source 12 may use any light emitting device 28 which provides an output of light at the requisite power, wavelengths and spectral sharpness. Glucose is a dilute constituent of blood. Due to this fact, when measuring the concentration of glucose in blood, there are a limited number of light emitting devices that meet all of these criteria and which have acceptable efficiency.

15

20

Light emitting diodes (LEDs) are one suitable light source which may be used in place of one or more of the laser diodes 30. Some LEDs may require a spectral filter, such as a narrow band filter, while others may be used without a spectral filter. A disadvantage of LEDs is that they are less efficient than laser diodes, particularly after the requisite spectral filtering is provided. In addition, LEDs are high divergence devices and are difficult to couple to an optical fiber with efficiencies much greater than 20%. Some advantages of LEDs over laser diodes are that they are inexpensive and the entire spectrum from 800 nm through 2,500 nm is commercially available.

25

Perhaps the most important decision in the design of an infrared spectroscopic chemical sensor is the choice of spectral region(s) and wavelengths, particularly if a white light source is either impractical or substantially non-optimal. The choice of wavelengths and spectral region(s) ultimately determines both the hardware and the software in (vitro algorithm). For an in vivo set-up, in general, the absolute minimum number of wavelengths is three points (unless one can use other means to pull out background, scattering, absorption by other constituents such as

using the pulsatile component as in the pulse oximeter). At least one point is needed for pathlength calibration and another two points are needed for measuring the height of the absorption peak. In complex media, such as blood, where there are a number of overlapping constituents, the number of requisite wavelengths increase substantially.

5 As a general rule, one can expect to add one or two spectral points for each chemical constituent whose concentration varies independently and which has some spectral structure in and around the absorption peak(s) used for determination of the constituent of interest. For near IR determination of the concentration of blood glucose, one needs additional spectral points to compensate for the overlapping globulin, cholesterol, 10 albumin, urea, hemoglobin, uric acid, and of course, water. In addition, there are no doubt other chemical species for which one also has to compensate. The means to choose the wavelengths are discussed below.

15 The selection of the spectral region(s) to be emitted by the source 12 depends upon the fluid constituent being measured, the availability of light sources and suitable detectors, water absorption and noise considerations. In general one chooses spectral regions in the vicinity of the absorption band(s) of the constituent(s) being measured. For example, the strongest glucose bands are around 10,000 nm, followed by the bands at about 2240 and 2080 nm, finally followed by a still weaker band at 1600 nm. Many other blood constituents show similar absorption patterns. On the 20 other hand water absorption and device constraints, particularly the availability of diodes and uncooled sensitive detectors, become very problematic beyond 2,500 nm. As discussed above, the photodetector 44 must have a five decade dynamic range to accurately determine glucose. For an implantable device which cannot be 25 cryogenically cooled, the linearity requirement mitigates against the use of wavelengths above 3,000 nm for constituents of low concentration since uncooled detectors do not have suitable performance characteristics above this wavelength.

Furthermore, water absorption becomes substantially more problematic beyond 2,500 nm. Light energy at 10,000 nm experiences more than a 10 dB loss through a water layer of 0.1 mm, thereby making it very difficult to obtain an

acceptable signal to noise ratio for an implantable device. Hence, for the measurement of glucose as well as most other blood constituents, it is generally preferable to use light less than 2,500 nm, even though there is substantial spectral information beyond 2,500 nm for most blood constituents. Even below 2,500 nm, 5 there are some bands of water absorption which can cause excessive attenuation for longer pathlengths; one at 1,899 nm and another at 1,454 nm.

Referring to Fig. 5, the light emitting device 28 of Fig. 1 may also be a tunable laser 70 which is programmed to produce a repeating output at the desired wavelengths. A tunable laser inherently outputs collinear light with respect to the 10 plurality of wavelengths because there is only a single output. Thus, the output of the tunable laser 70 may be coupled directly into the input end of optical fiber 34 of Fig. 1. As with the laser diode array 28, the entire desired spectra should be taken within substantially the same period of time. The calibration detector 40, collection detector 15 16, processor 18 and related components are not shown in Fig. 5 and may be the same components as those of Fig. 1.

Furthermore, the light emitting device 28 may be a white light source, such as a white light source having maximum output power in the near-infrared region. A white light source also inherently outputs light having wavelengths which are collinear with each other because there is only a single output. Thus, the output of the 20 white light source may also be coupled directly into the input end of optical fiber 34 of Fig. 1. When using a white light source, it is necessary to spectrally separate the output of the white light source to obtain spectral information for desired wavelengths. In one technique, shown in Fig. 6, a tunable spectral filter 72 is disposed between 25 white light source 74 and the photodetector 44, such as between the output of the white light source 74 and the input end of the optical fiber 34. The tunable spectral filter 72 is programmed to produce a repeating output at the desired wavelengths. As with the laser diode array 28, the entire desired spectra must be taken over a substantially single period of time. To conserve energy, the white light is pulsed on only when it is

desired to take a spectra. The tunable spectral filter 72 may be implemented by either a rotating disk with various spectral bandpass optical filters or by a rotating grating which couples the desired spectra into the optical fiber 34.

5 In another technique, shown in Fig. 7, a fixed grating 76 is disposed at the input of a photodetector 78 to spectrally separate the broadband white light into different spatial packets related to the thirteen wavelengths. (The photodetector 78 replaces the photodetector 44 in Fig. 1.) The photodetector 78 is constructed of an array of photodetectors 80₁-80₁₃, wherein each photodetector 80 detects one of the thirteen wavelengths. Since each photodetector 80₁-80₁₃ in Fig. 7 is coupled to the 10 same collection optical fiber 42, the requirement that light at each wavelength spatially overlaps each other is met.

15 The sensors in Figs. 5 and 6 include similar calibration detector, collection detector and processor components as in Fig. 1. Only the collection optical fiber 42 is shown in these figures. Likewise, the sensor in Fig. 7 includes similar calibration detector and processor components as in Fig. 1. The collection optical 42 fiber in these figures is a multimode fiber, typically having a diameter of 0.5 mm or greater, if non-linearity due to pathlength variations over the fiber aperture do not 20 present a problem.

25 Light having a plurality of different wavelengths which traverse substantially the same optical path (and which are thus collinear) is most easily produced by the source configuration of Fig. 1 wherein a plurality of single mode fibers are coupled to one single mode fiber via a Bragg diffraction grating. The amount of spatial overlap of the light required amongst the various wavelengths with respect to one another is a function of how strong a signal is produced by the desired fluid constituent and the expected degree of spatial inhomogeneity. Blood and most other human tissue tends to be highly spatially inhomogeneous, primarily due to scattering. For example, a 1 mm path of blood with a 100 mg/dl glucose concentration produces a peak absorption on the order of 10⁻⁴ at 2,273 nm (due to the glucose). Two

wavelengths, separated by 0.1 mm could create an apparent signal of 3×10^{-4} if the variations in scattering are on the order of 1% per mm. For example, if there is a spatial variation in scattering of the order of 1% per mm, and two wavelengths of light are separated by 0.1 mm, the detector 16 would have difficulty seeing the glucose absorption peak over the variability in scatter.

5 As discussed above, a white light source does not present a problem with respect to collinearity, but care must be taken to ensure that the spatial relationship between the source and the detector is constant during the time a spectra is taken.

10 Other techniques may be used to produce the desired collinear source beam from LEDs or individual laser diodes without using gratings or long optical fibers. For example, the LEDs or laser diodes may be physically located very close to each other so that the optical path of each wavelength of light is substantially collinear with each other with respect to the fluid that receives the light. Also, a negative lens or aperture may be used to improve collinearity.

15 In an alternative embodiment of the invention, each individual light source in the light source 12 may be frequency modulated at a unique predetermined frequency. If a frequency modulation scheme is used, all of the individual light sources may be pulsed simultaneously, thereby guaranteeing that the output of the light source 12 is temporally coincident amongst the plurality of wavelengths.

20 The sensors of Figs. 1-7 are extravascular, although they may be used intravascularly. However, intravascular sensors are not preferred because of potential clinical and technical complications, such as thrombosis and rejection. Alternatively, the sensors could be placed within a bone. However, the threat of infection is much greater in bone than in other internal body locations.

25 The sensors of Figs. 1-7 are arranged to measure light from the source which passes directly through the vein 14 or other anatomical structure. However, the sensors may also be arranged to detect reflected or scattered light, or combinations of transmitted, reflected or scattered light. It is currently believed that precise coupling

between the source 12 and the sample to be measured (vein 14 in Fig. 1) is more critical when relying upon reflected measurements than transmission measurements.

It is also believed that the signal to noise ratio obtainable with reflection spectroscopy in the measurement of blood glucose is lower than that obtainable with transmission spectroscopy in the near-infrared region.

The sensors of Figs. 1-7 are suitable for a wide range of in vivo environments, such as veins, vascular membranes, muscles, arteries and the like. To obtain accurate in vivo measurements of fluid constituents from certain types of environments, it may be necessary to protect the sensor components (especially the source output and detector input) and/or the sensing area from exposure to unwanted constituents, particularly when measuring fluid constituents in interstitial fluid.

It is known that glucose concentration in interstitial fluid may be accurately correlated with blood glucose levels and used for diabetes control and management. For example, it is known that glucose levels in interstitial fluid lag glucose levels in blood by about 20 minutes. When measuring glucose concentration, interstitial fluid has many advantages over blood. Interstitial fluid and gel have little or no hemoglobin and red blood cells, both of which create artifacts in spectroscopic measurements. For example, red blood cells cause scattering. By measuring in interstitial fluid, other sources of potential artifacts present in blood measurements may also be eliminated, including artifacts from pulsating blood vessels and the confusion of glucose spectra with hemoglobin spectra. Pathlength variability is not as significant in measurements taken in interstitial fluid, as opposed to blood measurements. Interstitial fluid may also have a lower protein concentration than blood, thereby making it easier to discern glucose from the blood spectra with greater predictive accuracy. Fewer source wavelengths are thus required to obtain accurate concentrations.

Fig. 8 shows a sensor 100 suitable for use in monitoring a fluid constituent in interstitial fluid 102. Interstitial regions contain interstitial gel consisting of interstitial fluid and a solid material primarily composed of collagen fibers. At times, debris may float within the interstitial region. The debris, adjacent tissue and

5

10

solid material (hereafter, "tissue and debris") may reduce the accuracy of measurements if they enter the measurement zone. The sensor 100 is constructed to block such constituents from entering a measurement zone or chamber 104 between a source 106 and a detector 108. The sensor 100 includes a barrier or jacket 109 having a wall or barrier 110 and end caps or lids 112, 114. The wall 110 is constructed of an inert biocompatible material having a porosity selected to allow the interstitial fluid and gel to pass therethrough (good interchange of fluid), while blocking adjacent tissue and debris. Suitable materials for constructing the wall 110 include polytetrafluoroethylene (e.g., TEFLON[®]) having plural perforations therethrough, porous ceramic and a biocompatible mesh material. The lids 112 and 114 may be constructed of an inert hermetic biocompatible material, such as titanium. The jacket 109 is preferably cylindrical, although other shapes are suitable.

15

A barrier 110 constructed of biocompatible mesh material will inhibit adjacent tissue from squeezing through the barrier 110, but will not inhibit encapsulation tissue from growing on the sensor components unless the mesh material is extremely fine and blocks the proteins and white blood cells from passing therethrough.

20

Alternatively, the barrier 110 may be constructed of a biocompatible wire screening which forms a shield or cage that is fine enough to prevent adjacent tissue from squeezing into the sensor chamber 104 and interfering with light transmission. Of course, this scheme will not prevent encapsulation tissue from growing on the sensor components.

25

Fig. 8 shows adjacent tissue and debris molecules 116 which cannot penetrate through the barrier 110, whereas glucose molecules 118 within the interstitial fluid 102 may penetrate through the barrier 110 and enter the chamber 104. Since the interstitial fluid 102 passes freely through the barrier 110, the concentration of glucose within the sensor 100 and in the area surrounding the sensor 100 is substantially the same. In Fig. 8, the source 106 may include any of the direct light emitting sources

5

described above, or the source 106 may be the output end of an optical fiber connected to a light emitting source. Likewise, the detector 108 may be any of the photodetector(s) described above which are compatible with the respective source, or the detector 108 may be the input end of a collection optical fiber connected to one or a plurality of photodetectors. If the source 106 and detector 108 are the optical fibers, the light emitting sources and the photodetector(s) may be remote to the jacket 109. The source 106 and the detector 108 are attached to respective ends of the jacket 109.

10

15

Regardless of whether the source 106 and detector 108 in Fig. 8 are directly coupled or coupled via an optical fiber delivery system, to minimize degradation of the source 106 and detector 108, it is necessary to provide them with respective hermetic jackets 126 and 128 and biocompatible, hermetically sealed transparent windows 130 and 132. The hermetic jackets 126 and 128 are constructed of any suitable inert, biocompatible material, such as titanium. The jackets 126 and 128 block all substances and constituents of the interstitial fluid from contacting sensor components. To further minimize growth of encapsulation tissue, a coating of hydrogel or similar material may be added to the windows 130 and 132, as well as to the jackets 126 and 128.

20

25

TEFLON[®] does not wet. Thus, if TEFLON[®] is used to construct the jacket 109, the sensor chamber 104 may be filled with alcohol or a saline solution prior to insertion of the sensor 100 into the interstitial fluid. Alternatively, the sensor chamber 104 is pressurized with the solution immediately after insertion. In either case, the solution gradually exchanges itself with the fluid outside the chamber and the inside of the chamber reaches equilibrium with respect to the outside of the chamber. An insertion spout 119 may be provided through one of the lids 112 or 114 to facilitate chamber filling.

Fig. 9 shows another embodiment of an open sensor 120 suitable for use in an interstitial fluid environment. This sensor 120 includes a source 106 and a detector 108 similar to those in Fig. 8, which are protected by similar jackets 126 and

128 and optically transparent windows 130 and 132. The output of the source 122 and the input of the detector 124 are spaced from each other by a predetermined distance. A rigid coupler 125 attached to the jackets 126 and 128 maintains the predetermined distance between the source 122 and the detector 124.

5 In Fig. 9, the source 122 may be a direct light emitting source or a plurality of sources, as described above, and the detector 124 may be a single photodetector or a plurality of photodetectors, as also described above. Alternatively, the source 122 and detector 124 may be optical fibers connected to respective light emitting source(s) and photodetector(s), wherein the optical fibers function as a light delivery system. In the latter case, the light emitting source(s) and photodetector(s) 10 may be remote from the open sensor 120.

15 Other techniques may be used in any of the embodiments shown in Figs. 1-9 to prevent or inhibit encapsulation tissue from growing on or around sensor components. Examples of potentially suitable schemes include using heat, electric fields, or electric current, either constantly or sporadically. For example, protein becomes denatured at 60°C. Thus, a daily heat blast lasting for a few seconds may be sufficient to prevent growth. One alternative technique to a physical barrier which minimizes the problem of adjacent tissue getting in between the source and detector is to physically place the sensor in the interstitial fluid environment so that the sensing 20 chamber is a significant distance away from the adjacent tissue.

25 The spectral information obtained at the output of the photodetector 44 or its equivalent is delivered to the processor 18 for spectral analysis. As discussed above, the processor 18 also receives a signal from the calibration detector 40. When measuring blood constituents using the sensor 10 of Fig. 1, the signal received from the photodetector 44 contains spectral information from all substances which received light from the source 36. Thus, there is spectral information from the fluid of interest (e.g., blood) as well as spectral information from extraneous tissue, including the vein wall of the vein 14 and the encapsulation tissue 48. There may be additional spectral

information from interstitial fluid and gel disposed between the sensor 10 and the vein 14. Hereafter, the spectral information associated with the fluid of interest is referred to as the "spectra of the fluid" or "fluid spectra", whereas the spectral information associated with extraneous tissue, including the vein wall of the vein 14 and the encapsulation tissue 48, and any solids within the interstitial gel is referred to as the "spectra of tissue" or "tissue spectra." The combination of both spectra is referred to herein as the "composite spectra." One goal of the processor 18 is to extract the fluid spectra from the composite spectra and to use the fluid spectra to obtain the concentration of the fluid constituent of interest or alternatively, to correct for the contributions of the tissue spectra to obtain accurate predictions of the constituent concentration.

Fig. 10 is a flowchart of the steps performed in the processor 18 using sensor 10 of Fig. 1. Generally, the processor 18 takes spectral data output from the detector 16 and applies an in vitro algorithm to determine the fluid constituent(s) of interest. The in vitro algorithm is generated by correlating the Fourier Transform Infrared (FT-IR) spectroscopy transmission measurements of fluid samples from a statistically significant number of people to fluid samples measured using conventional techniques (i.e., techniques other than the technique of the present invention). A statistical model is applied to the FT-IR data, and the in vitro algorithm is optimized for the best least-squares prediction error and the least number of spectral points. The in vitro algorithm therefore determines the spectral points to be measured and their relative weighting of absorptivity. The algorithm is then applied to the in vivo measured spectral data to determine the concentration of selected fluid constituent(s).

Referring to Fig. 10, the processor 18 computes the absorbance spectra by taking the log of the ratio of the output of the detector 16 and the output of the calibration detector 40 for each wavelength (step 100) and adding a correction factor (step 200) to correct for (1) variability in responsivity between the detectors 16 and 40,

and (2) chromatic differences in the optical systems. The resultant signal is the composite absorbance spectra or simply "composite spectra" referred to above.

Next, the processor 18 applies an in vitro algorithm, defined by steps 300-600 within dashed lines in Fig. 10, to the composite spectra. The first step in the 5 in vitro algorithm is to apply a pathlength correction to the composite spectra (step 300). One method of performing this step is to divide the composite spectra by the difference in absorbance of the composite spectra at two wavelengths, suitably chosen for pathlength normalization. Another method is to divide the composite spectra by the "computed pathlength" as determined by a Partial Least Squares algorithm.

10 After the pathlength correction is completed, the processor 18 applies a baseline correction to the composite spectra (step 400). One method for performing a baseline correction is by subtracting the absorbance (also pathlength corrected) at a third wavelength from the pathlength corrected composite spectra. The resulting composite spectra is now both pathlength and baseline corrected. Alternatively, the 15 baseline correction may be applied before the pathlength correction by reversing the order of steps 300 and 400.

20 Next, the processor 18 computes an "uncorrected" concentration of the desired constituents by multiplying the pathlength-and-baseline-corrected composite spectra by beta coefficients (step 500) and then adding a constant to the result (step 600). The concentration is referred to as "uncorrected" because the beta coefficients 25 are applied to the composite spectra which includes the extraneous tissue spectra, and not just the fluid spectra of interest.

DETERMINATION OF THE IN VITRO ALGORITHM

25 The preferred embodiment of the invention uses the Norris regression model to generate the optimum in vitro algorithm. Also, in the preferred embodiment of the invention, the choice of wavelengths and their corresponding beta coefficients are determined on an in-vitro basis, and ideally on a cross-population basis. Fluid

samples representative of the fluid being measured are collected from a statistically significant group of people, such as a few hundred people. Care should be taken to avoid altering the chemistry of the fluid samples due to exposure to air, time, and the like. Ideally, the chemical constituents of both the desired constituents and other constituents which affects the spectra span essentially the entire physiological range for both healthy and sick individuals. It is also important that other physiological variables such as temperature and pH span the entire physiological range so that the calibration model holds true over a wide variation of patient health conditions.

After the fluid samples are collected, a spectra of the fluid is taken using a conventional spectrophotometry technique, such as by using a scanning or FT-IR spectrophotometer having a white light source. In addition, the concentrations of the desired constituents (e.g., glucose) are also measured by a conventional non-spectroscopic means, such as chemical assay. To allow for pathlength correction, cuvettes of several pathlengths should be used, covering the range of pathlengths ultimately being measured *in vivo*.

When generating the *in vitro* algorithm for application in steps 300, 400 and 500, the wavelengths used for pathlength correction, baseline correction and beta coefficients are preferably reiteratively optimized to provide the least-squares fit. However, before this optimization is performed, some initial guesses must be made for the wavelengths.

For the pathlength correction, which requires at least two wavelengths, the guess for the first wavelength may be obtained by computing the correlation coefficient for the spectra obtained from the *in vitro* samples with the measured pathlength, and choosing the coefficient which gives a correlation as close as possible to unity. The guess for the second wavelength may be obtained by computing the correlation coefficient of each wavelength of the spectra divided by the difference between the absorbance at each wavelength and the absorbance at the first wavelength with measured pathlength, and again choosing a correlation coefficient as close as possible to unity.

The actual pathlength correction involves dividing the absorbance spectra with the difference in absorbance at the first and second wavelength, as described above.

For the baseline correction, the initial guess for the offset wavelength may be empirically determined by looking at the spectra and then choosing a wavelength in a region of greatest flatness.

For the beta coefficients, the initial guesses for the wavelengths may be determined by computing the correlation of the measured constituents with the spectra and choosing wavelengths with correlation coefficients that are as close as possible to +1 or -1. It is also possible to obtain even better guesses for initial wavelengths by using wavelengths which have the largest beta coefficients (in absolute value), as determined in a Partial Least Squares (PLS) routine.

The beta coefficients are chosen by finding coefficients which provide a best least-squares fit of the spectra at the initially guessed wavelengths to the measured concentration of the constituents. Once the beta coefficients are optimized for the initial "guessed" wavelengths, the process is repeated, sequentially varying each wavelength and reoptimizing the beta coefficients to produce the best least-squares fit, thereby obtaining an optimized set of discrete wavelengths and corresponding beta coefficients. Ultimately, the standard error of calibration tends to asymptotically approach some minimum value.

The process described above provides an in vitro algorithm for calibrating the measured spectra at a finite number of wavelengths to the measured concentration (steps 300 and 400) and for computing an uncorrected concentration of desired constituents (steps 500 and 600). After these steps are performed, it is still necessary to correct for tissue spectra and obtain "corrected" concentrations.

In an implantable sensor, there is invariably extraneous tissue surrounding the fluid which contains the desired constituents and which creates the issue spectra. There are variations from person to person in both chemical composition

5

and thickness of the encapsulation tissue, as well as in other extraneous tissue. In general, the extraneous tissue alters the spectra taken by the sensor. Unless some method is used to compensate for the extraneous tissue, it will cause an error in the computed concentrations of chemical constituents because the in vitro algorithm was developed using in vitro fluid samples (which do not have extraneous tissue). However, as long as the encapsulation tissue is stable with time, one can completely compensate for such tissue.

METHODS TO GENERATE ALGORITHM TO ACCOUNT FOR OR COMPENSATE FOR EXTRANEous TISSUE

10

In one preferred compensation method, a best linear fit on each individual patient is performed of the uncorrected concentration of the constituents (output of step 600) to the concentrations measured in vitro by conventional means, and a set of best linear fit coefficients is obtained. This measurement should be done after a period in time sufficiently long for the encapsulation tissue to reach steady-state (typically, greater than four weeks). These coefficients are stored in the processor 18 for step 700. The coefficients are applied to the uncorrected concentration of constituents to obtain predicted concentrations which are "corrected" for the extraneous tissue (step 700).

15

To obtain the most accurate calibration of the uncorrected concentrations to the corrected concentrations, the concentrations of the desired constituents for a particular patient should span the likely range of measurement.

20

For example, if the sensor is a blood glucose sensor, the calibration should be done over a range of glucose values ranging from 25 mg/dl to 300 mg/dl.

25

ALTERNATIVE EMBODIMENTS TO DETERMINATION OF THE IN VITRO ALGORITHM

An alternative approach to determining values for the in vitro algorithm is to apply multivariate analysis using PLS optimization to the in vitro data. The exact same in vitro data is collected (spectra, concentrations and pathlengths) on a cross-population basis as described above in the section labeled "DETERMINATION OF THE IN VITRO ALGORITHM". In one example, a PLS routine from Galactic Industries, Salem, New Hampshire, corrects for pathlength variability by using the measured pathlength as the first constituent and the other measured constituents as second and greater constituents. Initially, the entire spectral region may be used. Next, the routine determines the standard error of prediction on a cross-calibration approach and the beta coefficients for both pathlength and for each chemical constituent.

When using this alternative approach, steps 300, 400 and 500 in Fig. 10 are modified as follows:

Step 300 (pathlength correction) - (1) determine pathlength by applying the beta coefficients for pathlength determined above to the composite spectra, and (2) divide the composite spectra by the computed pathlength.

Step 400 (baseline correction) - This step is optional and may be performed before or after step 300.

Step 500 - Apply the beta coefficients as determined above in the PLS algorithm to the pathlength corrected composite spectra.

In the PLS technique, use of the entire spectral region as measured by a spectrophotometer typically does not yield the best predicted error or standard error of calibration, nor is it the most efficient method. Improvements in both accuracy and efficiency of the in vitro algorithm are possible by choosing spectral regions where the beta coefficients are the greatest and eliminating spectral regions where the beta coefficients are the smallest. This process involves reiteratively optimizing selected spectral regions and finding a limited number of spectral points which yield adequate cross-calibration and predicted error. Ideally, as few spectral points as possible should be chosen, consistent with a low cross-calibration error, to minimize the cost and

complexity of the sensor. For example, each spectral point may correspond to a different diode.

Other statistical models which may alternatively be used for generating the optimum algorithm include Principal Component Regression, Neural Networks, and combinations of all of the above-described models. Second derivative data is used to minimize problems with baseline shift and spectral structure enhancement caused by scattering and pathlength variability.

ALTERNATIVE METHODS TO CORRECT FOR EXTRANEous TISSUE

The most obvious method to correct for extraneous tissue is to choose wavelengths for the in vitro algorithm in which the composite spectra is not particularly affected by the extraneous tissue. In many cases, this may not be possible. Hence, a correction such as step 700 in Fig. 10 must be performed.

Another possible method to correct for the extraneous tissue is to subtract a "representative spectra" of the extraneous tissue. This method involves adding an additional step between steps 200 and 300 of Fig. 10. The representative spectra of the extraneous tissue would be subtracted from the composite spectra to obtain a spectra representative of the fluid alone. The "representative spectra" (obtained as described below) would be patient specific. Steps 300 through 600 would be applied to the "fluid spectra" rather than the composite spectra in Fig. 10. Step 700 would be deleted as it would not be necessary.

The representative spectra may be obtained in several ways. One way is to take a number of in vitro fluid samples on each patient after the sensor has been implanted for a period of time sufficiently long for the encapsulation tissue to reach steady-state. Simultaneous to the in vitro fluid samples being taken, the spectra of corresponding composite spectra would be taken by the implantable sensor. The spectra on the in vitro fluid samples would be taken using either an FT-IR, scanning spectrophotometer, or dedicated spectrophotometer similar to the implanted one. It can

be assumed that the representative spectra of the extraneous tissue is constant from sample to sample, for each patient. Hence, the representative spectra of the extraneous tissue can be found by finding the spectra which best fits the difference between the composite spectra and the product of a constant times the spectra of the corresponding in vitro fluid sample. The constant which is multiplied with the spectra of the in vivo fluid sample is to allow for variable in vivo fluid pathlengths, due to blood flow changes for example. The representative extraneous spectra is henceforth stored in the processor and used in the additional step.

The difficulty with this approach is that extreme care must be taken to ensure that the temperature at which the in vitro sample is taken is held to the same temperature as the corresponding in vivo sample.

A variation to the determination of the representative extraneous spectra is to take the spectra of representative constituents of the extraneous tissue such as a vein wall, collagen, and the like, and determine the best linear combination of these constituents which best fit the difference between the composite spectra and the product of a constant times the spectra of the corresponding in vitro fluid sample. Every other step is the same as outlined above.

Still another way to compensate for the contributions of tissue spectra when measuring across a pulsating blood vessel, such as an artery, is to take the composite spectra at the maximum and minimum of the pulse, and then subtract the two spectra. The subtracted spectra is essentially that of blood alone, although there is a small component due the change in thickness of the vessel wall.

PROCESSOR DETAILS

Referring to Fig. 1, the corrected concentrations of constituents may be shown on the display 20, used to trigger the alarm 22 or used to control a medication dispenser 23. The corrected concentration values, and the date and time of measurement may optionally be stored in a memory (not shown) associated with the

processor 18. The processor 18 may signal to the implantable sensor 10 via telemetry to make more frequent measurements if either the trending or the measured value of the constituents are determined to be problematic. Ideally, a physician would set alarm and measurement frequency parameters.

5 The processor 18 also detects "outlier data," which is data that falls outside of preset bounds due to a sensor malfunction). If outlier data occurs, the processor 18 telemeters the sensor 10 to take another measurement, and triggers the alarm 22 if subsequent measurements are also outside of preset bounds.

10 The processor 18 may be sporadically calibrated against conventionally obtained fluid constituent measurements to prevent long-term drift. For example, when the sensor 10 is used for glucose monitoring, the processor 18 may be sporadically calibrated against blood glucose measured by chemical assay. One form of this calibration may be to supply a new set of best linear fit coefficients of step 700.

15 If the processor 18 is used for feedback control, the processor output signal may be used to directly control the dispenser 23, or the dispenser 23 may have its own processor (not shown) for receiving the output signal and controlling the dispensed dose.

20 The present invention is particularly useful for detecting glucose concentration in blood and interstitial fluid. However, the invention may also be used to measure other body fluid constituents, including proteins, cholesterol, and other blood constituents.

25 It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the appended claims.

CLAIMS

1. A method of determining concentration of a constituent of body fluid in a mammal using *in vivo* spectroscopy, the method comprising the steps of:

- (a) implanting a sensor system in the mammal, the sensor system including a source of light which emits at a plurality of different wavelengths, at least one of the wavelengths being in the infrared region, and a detector for detecting light emitted from the source, the source and the detector located so that (i) the light output from the source interacts with a body fluid before being received by the detector, and (ii) light from each of the plurality of different wavelengths has a substantially collinear optical path through the fluid with respect to one another;
- (b) emitting light from the source;
- (c) obtaining a signal at the output of the detector which contains spectra of the body fluid at each of the plurality of different wavelengths; and
- (d) analyzing the signal to determine the concentration of the constituent of the body fluid.

2. A method according to claim 1 wherein step (a) includes positioning the sensor system so that the infrared light passes through body fluid containing the at least one constituent and extraneous tissue, step (c) includes obtaining a composite spectrum which includes spectra of the fluid and spectra of the tissue, the tissue spectra resulting from the extraneous tissue, and step (d) further includes correcting for the spectra of the tissue.

3. A method according to claim 2 wherein step (d) includes:

- (i) applying a pathlength correction to the composite spectra;
- (ii) applying a baseline correction to the composite spectra;
- (iii) multiplying the pathlength and baseline corrected composite spectra by beta coefficients and adding a constant thereto to obtain a concentration of the at least one constituent which is uncorrected for the tissue spectra; and

(iv) applying best linear fit coefficients to the uncorrected concentration of the at least one constituent of the body fluid to obtain a concentration of the at least one constituent which is corrected for the tissue spectra.

4. A method according to claim 3 further comprising, prior to performing step (d), determining the beta coefficients in vitro by the steps of:

(i) collecting in vitro fluid samples from a statistically significant plurality of mammals;

(ii) obtaining spectra of the fluid samples using a scanning or FT-IR spectrophotometer having a white light source;

(iii) correlating the spectra of the in vitro samples to the concentration of the at least one constituent measured using non-spectroscopic means; and

(iv) selecting a finite number of discrete wavelengths and respective beta coefficients which provide a best least-squares fit of the spectra of the in vitro samples to the measured concentration of the at least one constituent.

5. A method according to claim 4 wherein the step of selecting the beta coefficients and the respective discrete wavelengths further includes the steps of:

(v) initially guessing for the discrete wavelengths by either selecting wavelengths with correlation coefficients in step (iii) that are as close as possible to +1 or -1 or by selecting wavelengths which have the largest beta coefficients in absolute value as determined in a Partial Least Squares routine;

(vi) optimizing the beta coefficients for the initial guessed wavelengths; and

(vii) sequentially varying each wavelength and reiteratively optimizing the beta coefficients to produce the least-squares fit, thereby obtaining an optimized set of discrete wavelengths and beta coefficients.

6. A method according to claim 2 wherein step (d) includes:

- (i) subtracting a representative spectra of extraneous tissue from the composite spectra to obtain the fluid spectra;
- (ii) applying a pathlength correction to the fluid spectra;
- (ii) applying a baseline correction to the fluid spectra; and
- (iii) multiplying the pathlength and baseline corrected fluid spectra by beta coefficients and adding a constant thereto to obtain a concentration of the at least one constituent.

7. A method according to claim 1 wherein step (b) includes emitting light at the plurality of different wavelengths at a substantially single period of time.

8. A method according to claim 7 wherein the substantially single period of time is less than about 100 microseconds.

9. A method according to claim 1 wherein the body fluid is blood, and step (a) includes positioning the implantable sensor system extravascularly, the source and the detector being arranged so that the light output from the source interacts with a blood vessel before being received by the detector, and step (d) includes analyzing the signal to determine the concentration of at least one blood constituent.

10. A method according to claim 9 wherein step (d) includes analyzing the signal to determine the concentration of blood glucose.

11. A method according to claim 1 wherein the body fluid is blood, and step (a) includes positioning the implantable sensor system around a vascular membrane, the source and the detector being arranged so that the light output from the source interacts with the vascular membrane before being received by the detector, and step (d) includes analyzing the

signal to determine the concentration of at least one blood constituent in the vascular membrane.

12. A method according to claim 11 wherein step (d) includes analyzing the signal to determine the concentration of blood glucose.

13. A method according to claim 1 wherein the body fluid is interstitial fluid or gel, and step (a) includes positioning the implantable sensor system in a region of the body containing interstitial fluid or gel, the source and the detector being arranged so that the light output from the source interacts with the interstitial fluid or gel before being received by the detector, and step (d) includes analyzing the signal to determine the concentration of at least one constituent of the interstitial fluid or gel.

14. A method according to claim 13 wherein step (d) includes analyzing the signal to determine the concentration of glucose in the interstitial fluid or gel.

15. A method according to claim 1 wherein in step (b), the light emitted from the source has wavelengths in the near-infrared region.

16. A method according to claim 15 wherein all of the emitted wavelengths are in the near-infrared region.

17. A method according to claim 1 wherein step (b) includes sequentially emitting light at the plurality of different wavelengths from the source in a pulsed manner, light from all of the wavelengths being emitted within a substantially single period of time.

18. A method according to claim 1 wherein the detector of the sensor system is arranged to receive light transmitted through the fluid, and the signal obtained in step (c) includes the transmitted light.

19. A method according to claim 1 wherein the detector of the sensor system is arranged to receive light reflected or scattered by the fluid, and the signal obtained in step (c) includes the reflected or scattered light.

20. A method according to claim 1 wherein the source has a plurality of individual source elements, each source element emitting a different wavelength, and step (b) includes emitting the light from the plurality of individual source elements.

21. A method according to claim 1 further comprising the step of:

(e) measuring the output power of the source, wherein step (d) includes the step of obtaining an absorbance spectra by taking a log of the ratio of the detector output signal of step (c) and the output power of the source for each of the different wavelengths.

22. An implantable sensor adapted for determining concentration of a chemical constituent of body fluid in a mammal using in vivo spectroscopy, the sensor comprising:

(a) a source of light which emits at plurality of different wavelengths, at least one of the wavelengths being in the infrared region;

(b) a detector for detecting light emitted from the source and outputting a signal which contains spectra of the body fluid at each of the plurality of different wavelengths, wherein the source and the detector are located so that (i) the light output from the source interacts with a body fluid before being received by the detector, and (ii) light from each of the plurality of different wavelengths has a substantially collinear optical path through the fluid with respect to one another; and

(c) a processor for analyzing the signal and the spectra, and determining therefrom the concentration of the chemical constituent in the body fluid.

23. A sensor according to claim 22 further comprising:

(d) a controller for causing the source to emit light at the plurality of different wavelengths within a substantially single period of time.

24. A sensor according to claim 23 wherein the substantially single period of time is less than about 100 microseconds.

25. A sensor according to claim 22 wherein the source includes a plurality of individual source elements, each source element emitting light at a different wavelength in the infrared region.

26. A sensor according to claim 25 wherein the individual source elements include laser diodes.

27. A sensor according to claim 26 wherein the individual source elements include light emitting diodes.

28. A sensor according to claim 22 wherein the source includes:

(i) a plurality of individual source elements each emitting light at one of the different wavelength in the infrared region; and

(ii) single core multimode optical fiber for receiving the light at the plurality of emitted wavelengths, the output of the optical fiber being the emitted output of the source, wherein the optical fiber has a length sufficient to allow for substantial wavelength mixing as light at the plurality of emitted wavelengths travel through the optical fiber towards the output of the optical fiber, the wavelength mixing creating a substantially collinear optical path through the fluid for the different wavelengths with respect to one another.

29. A sensor according to claim 28 wherein the length of the optical fiber is greater than 1 meter.

30. A sensor according to claim 22 wherein the source includes:

(i) a plurality of individual source elements, each emitting light at one of the different wavelength in the infrared region; and

(ii) a diffraction grating coupler for receiving the light at the plurality of emitted wavelengths and outputting light at the plurality of different wavelengths in a substantially collinear optical path with respect to one another, the output of the diffraction grating coupler being the emitted output of the source.

31. A sensor according to claim 22 wherein the source includes a tunable laser for emitting light at the plurality of different wavelengths, the tunable laser being programmed to scan through the plurality of different wavelengths.

32. A sensor according to claim 22 wherein the source includes:

- (i) a broadband light which simultaneously emits light which includes at least the plurality of different wavelengths; and
- (ii) a tunable spectral filter disposed between the output of the broadband light and the output of the source, the tunable spectral filter being programmed to scan through the plurality of different wavelengths.

33. A sensor according to claim 22 wherein the source includes a broadband light source which simultaneously emits light having a spectra that includes at least the plurality of different wavelengths, and the detector includes:

- (i) a single collection optical fiber for receiving broadband light which has interacted with the body fluid;
- (ii) a fixed grating for receiving broadband light which has interacted with the body fluid and spectrally separating the received broadband light into a plurality of predefined wavelengths; and
- (iii) a plurality of photodetectors, wherein each photodetector detects light at one of the predefined wavelengths.

34. A sensor according to claim 22 wherein light at the plurality of different wavelengths are output in a time-sequenced manner, and the detector includes a single

photodetector which processes the light at the plurality of different wavelengths in coordination with the time-sequencing.

35. A sensor according to claim 22 wherein the source emits light at wavelengths in the near-infrared region from about 1,000 nanometers to about 2,500 nanometers.

36. A sensor according to claim 22 wherein the detector of the sensor system is arranged to receive light transmitted through the fluid, and the signal analyzed by the processor includes the directly transmitted light.

37. A sensor according to claim 22 wherein the detector of the sensor system is arranged to receive light reflected or scattered by the fluid, and the signal analyzed by the processor includes the reflected or scattered light.

38. A sensor according to claim 22 wherein the detector includes photodetector.

39. A sensor according to claim 22 wherein the source includes a plurality of individual source elements arranged in close proximity to each other relative to the distance between the individual elements and the detector, so that the plurality of source elements define the substantially collinear optical path.

40. A sensor according to claim 22 wherein the sensor includes a plurality of individual source elements, each individual source element being frequency modulated at a unique predetermined frequency.

41. A sensor according to claim 22 wherein the sensor includes a calibration detector for detecting the output power of the source, the detected output power being communicated to the processor for use in the signal analysis.

42. A sensor according to claim 22 wherein the processor includes an output signal for indicating that the concentration of the at least one chemical constituent is outside of a predetermined range.

43. An infusion pump system for monitoring at least one chemical constituent of body fluid in a mammal and delivering medication to the mammal, the system comprising:

(a) an implantable sensor adapted for determining concentration of a chemical constituent of body fluid in a mammal using *in vivo* spectroscopy, the sensor including:

(i) a source of light which emits at a plurality of different wavelengths, at least one of the wavelengths being in the infrared region;

(ii) a detector for detecting light emitted from the source and outputting a signal which contains spectra of the body fluid at each of the plurality of different wavelengths, wherein the source and the detector are located so that (1) the light output from the source interacts with a body fluid before being received by the detector, and (2) light from each of the plurality of different wavelengths has a substantially collinear optical path through the fluid with respect to one another; and

(iii) a processor for analyzing the signal and the spectra, and determining therefrom the concentration of the chemical constituent of the body fluid.

(b) a pump module connected to the sensor for dispensing doses of medicine in response to the concentration of the chemical constituent output from the processor.

44. A system according to claim 43 wherein the sensor further comprises:

(iv) a controller for causing the source to emit the light at the plurality of different wavelengths within a substantially single period of time.

45. A system according to claim 43 wherein the sensor determines the concentration of blood glucose in a body fluid of the mammal, and the medication dispenser is an insulin infusion pump for dispensing doses of insulin.

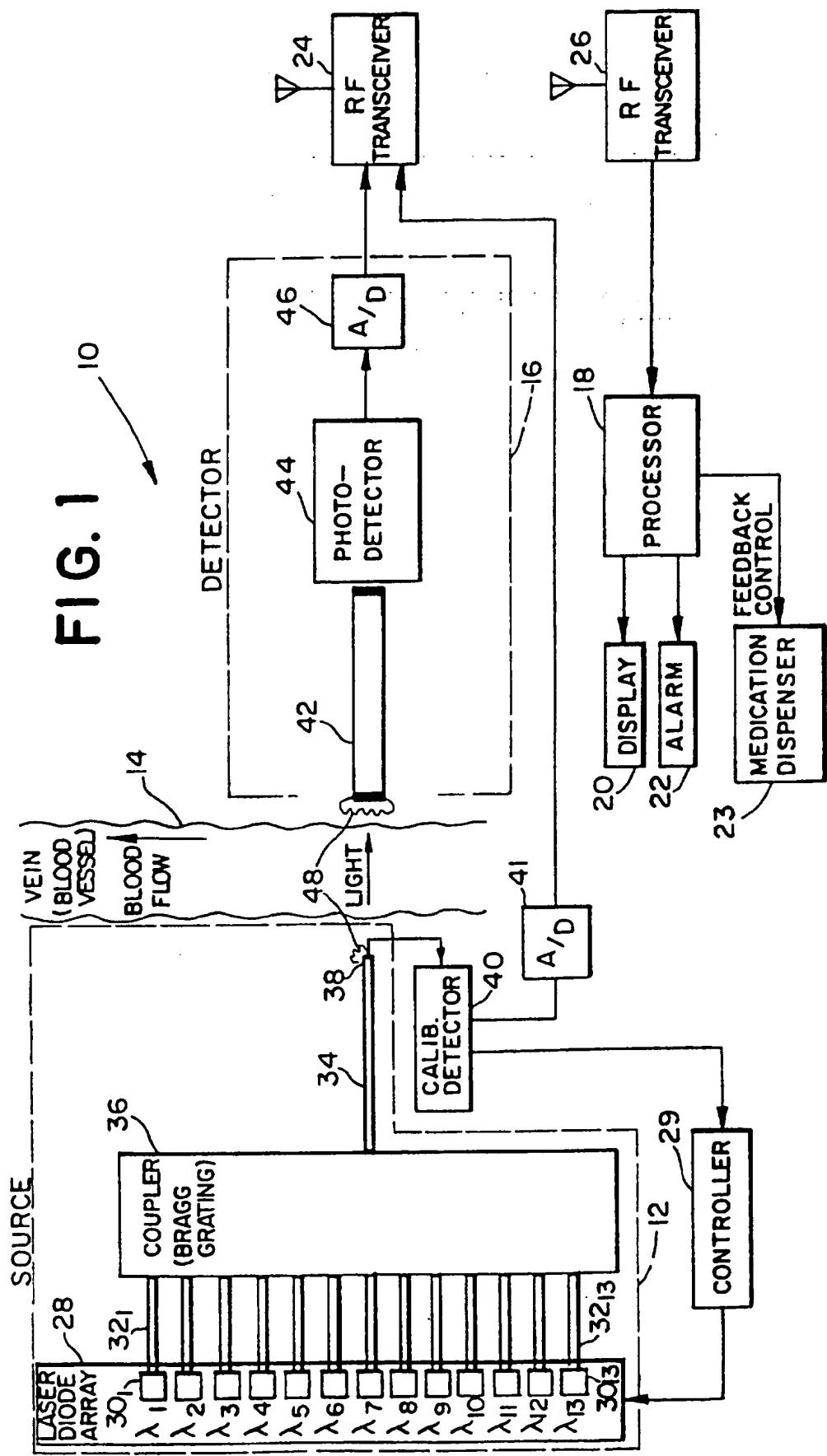
46. An implantable sensor adapted for determining concentration of a chemical constituent of body fluid in a mammal using *in vivo* spectroscopy, the sensor comprising:

(a) a chamber which has a porosity sufficient to allow interstitial fluid or gel to pass therethrough but which inhibits adjacent tissue and solid material from passing therethrough;

(b) a source of light disposed within the chamber that emits at a plurality of different wavelengths, at least one of the wavelengths being in the infrared region;

(c) a detector disposed within the chamber and spaced from the source for detecting light emitted from the source and outputting a signal which contains spectra of the interstitial fluid or gel at each of the plurality of different wavelengths, wherein the source and the detector are located so that (i) the light output from the source interacts with the interstitial fluid or gel before being received by the detector, and (ii) light from each of the plurality of different wavelengths has a substantially collinear optical path through the interstitial fluid or gel with respect to one another; and

(d) a processor for analyzing the signal and the spectra, and determining therefrom the concentration of the chemical constituent in the interstitial fluid or gel.



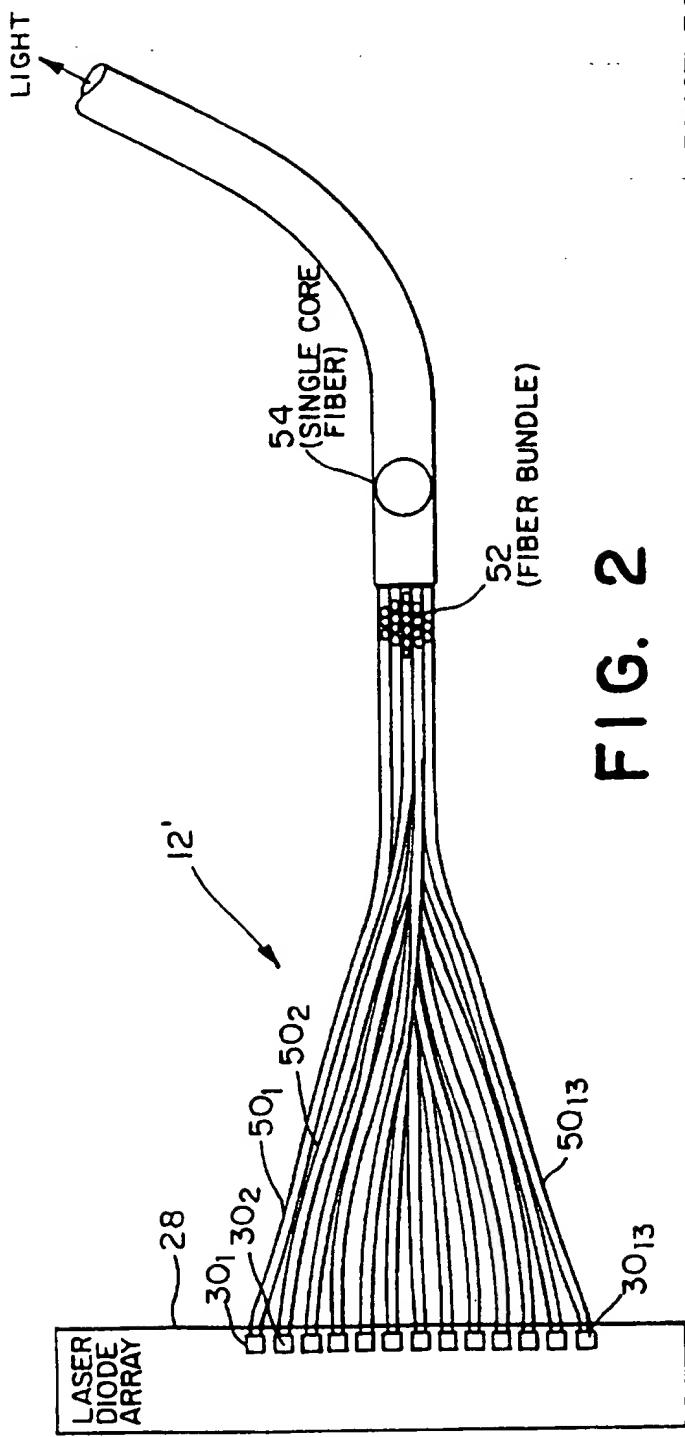


FIG. 2

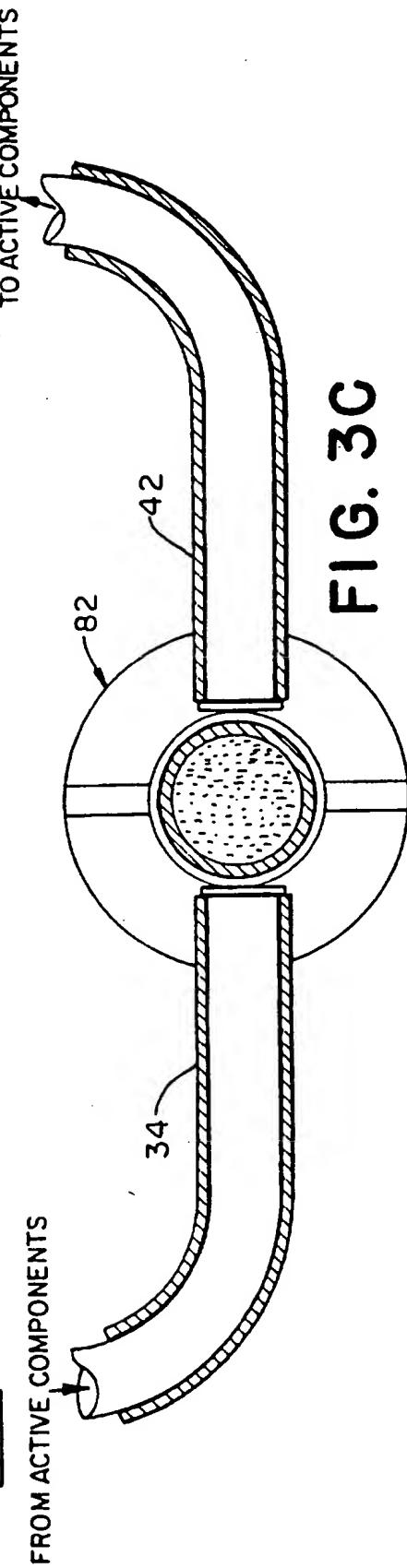


FIG. 3C

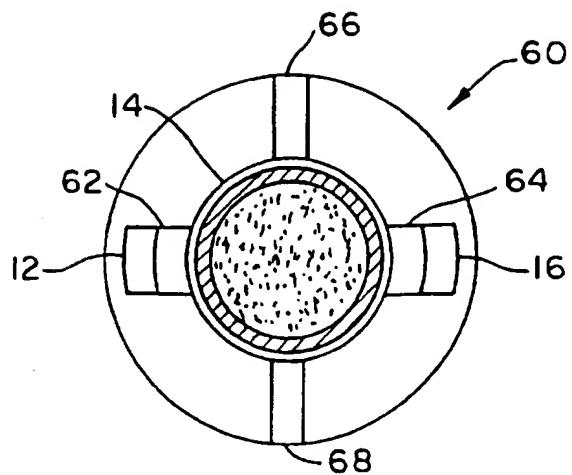


FIG. 3A

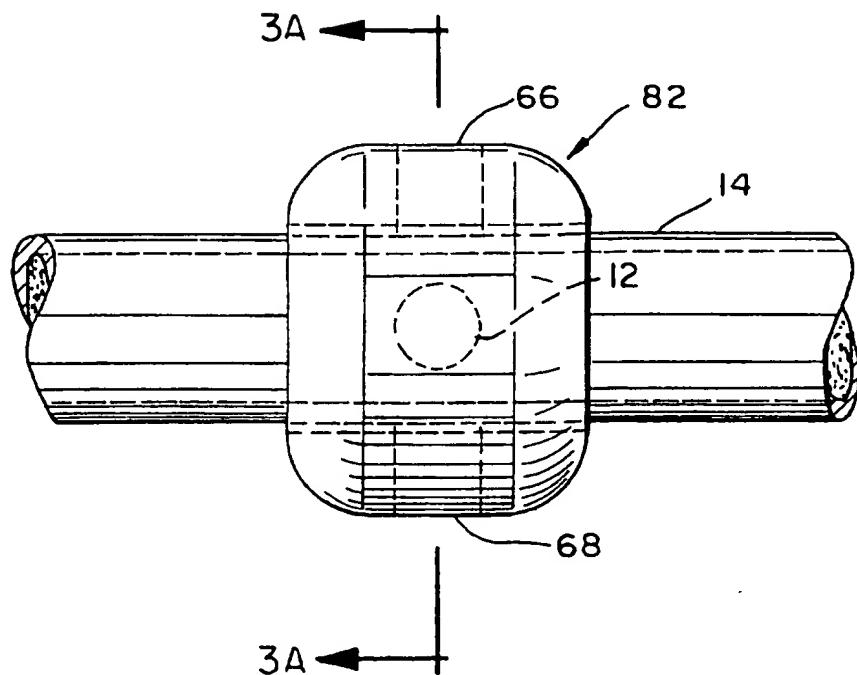


FIG. 3B

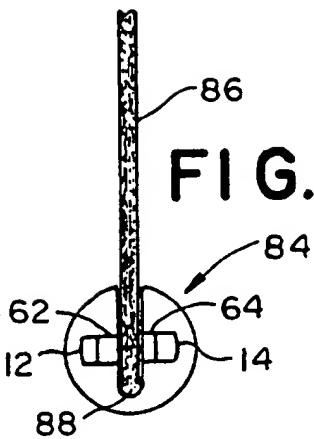


FIG. 4A

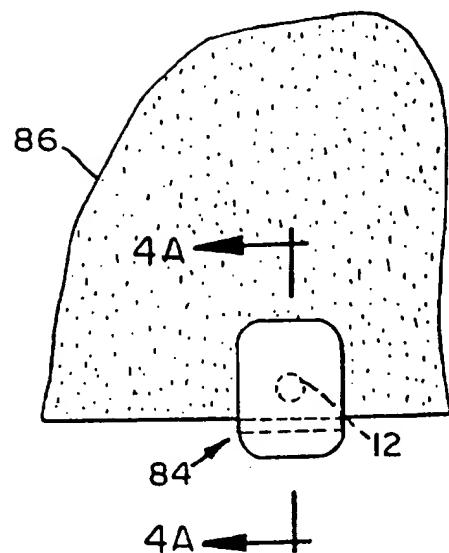


FIG. 4B

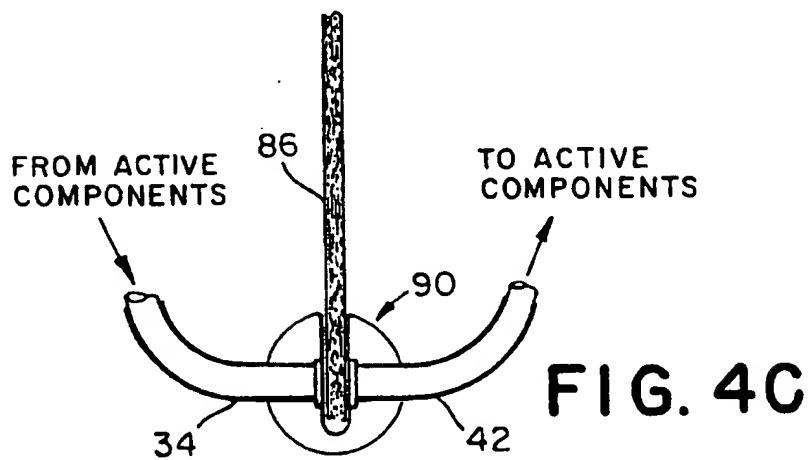
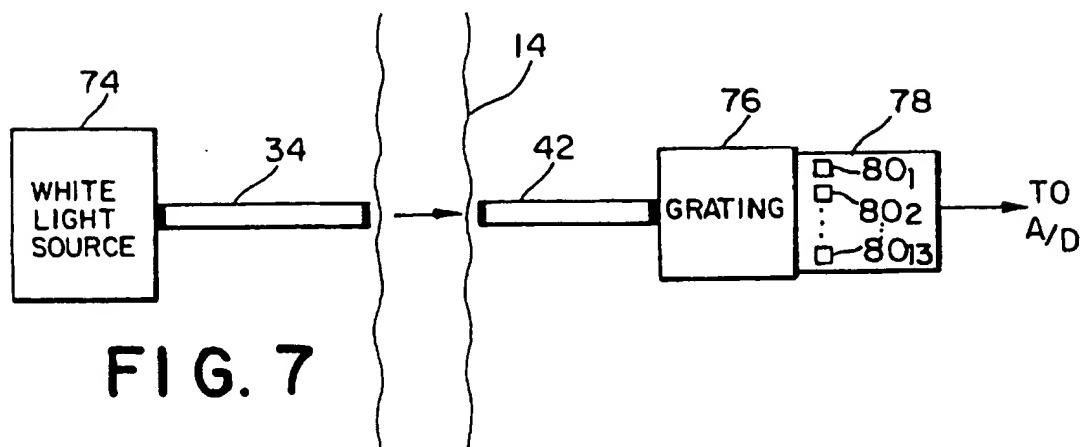
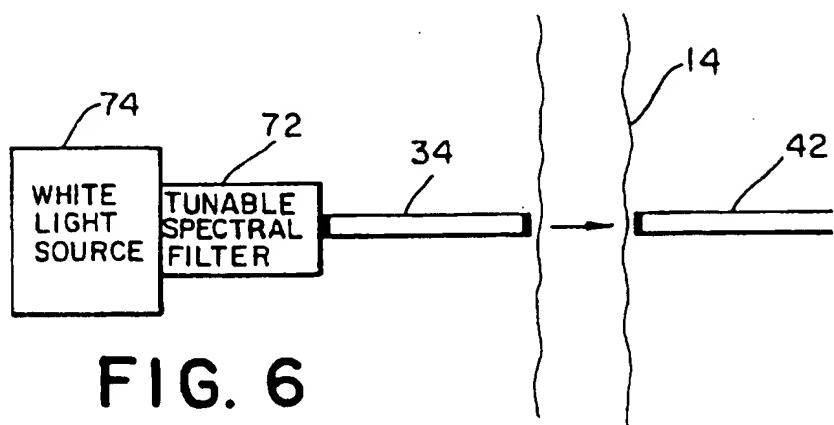
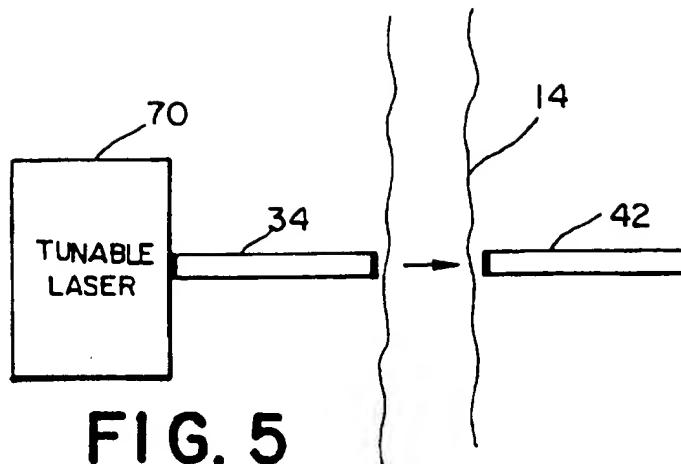


FIG. 4C



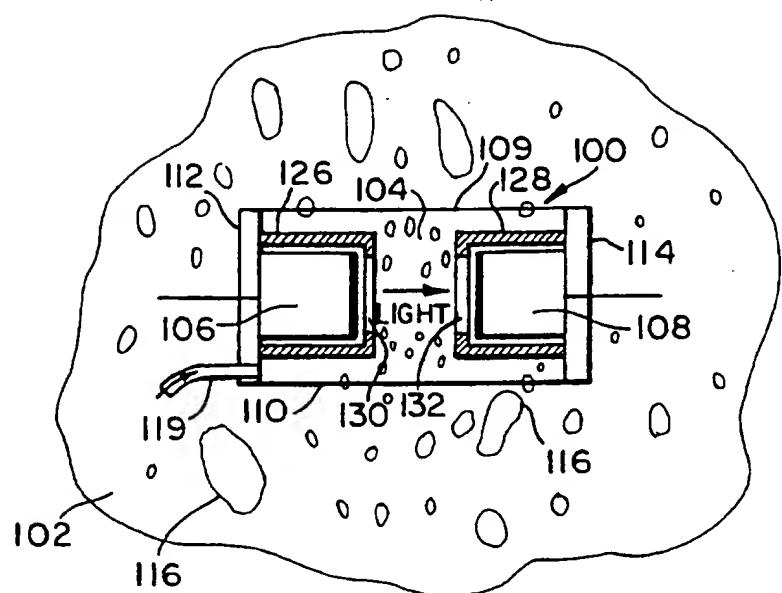


FIG. 8

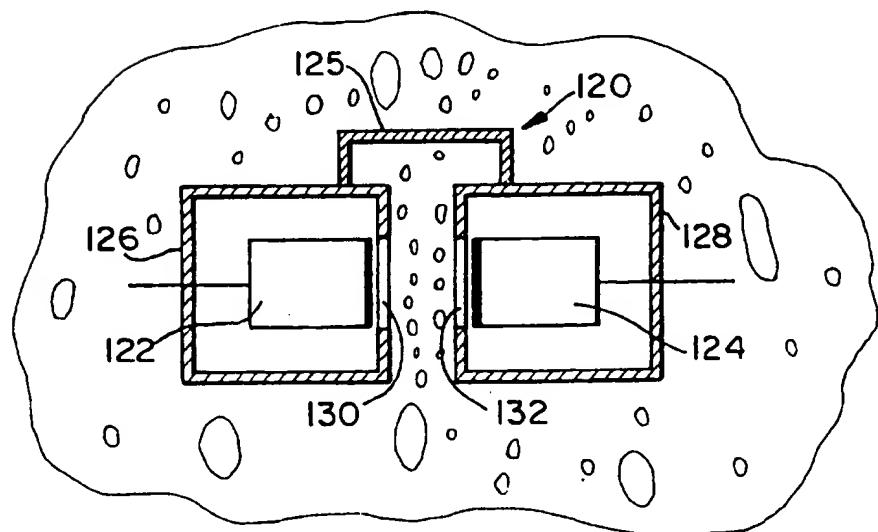


FIG. 9

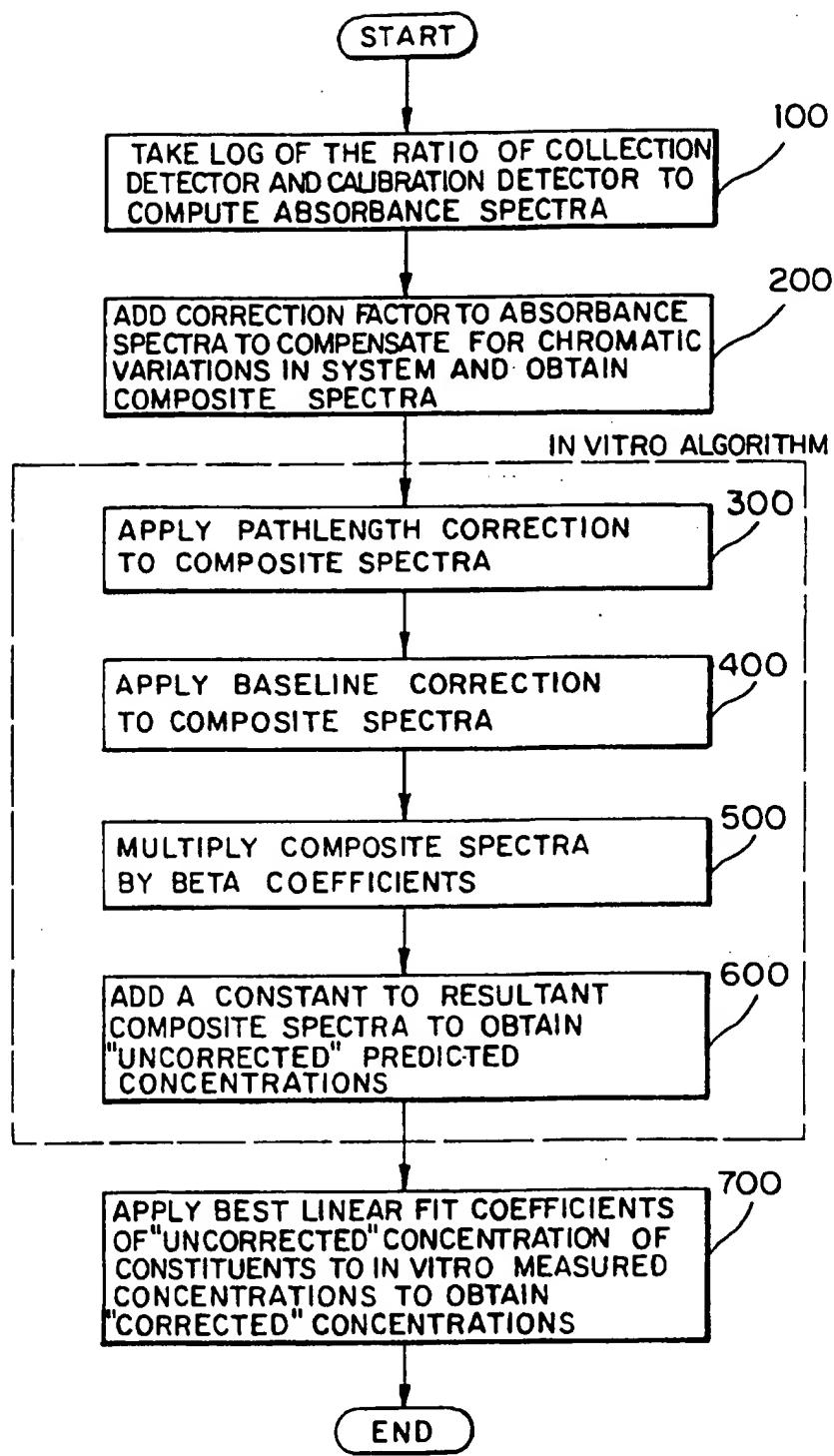


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/11832

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/00

US CL :128/633; 604/891.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/633, 634; 356/39; 604/50, 66, 67; 890.1, 891.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- P	US, 5,598,841 A (TANIJI et al) 04 February 1997, col. 6 line 50 to col. 7 line 43.	1, 7-9, 11, 15, 17-26, 28, 31, 32, 36-41
Y		----- 16, 27, 29, 34, 42
A	US, 5,474,552 A (PALTI) 12 December 1995, colu. 2 line 66 to col. 3 line 11.	43-45

Further documents are listed in the continuation of Box C.

See patent family annex.

•	Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12 AUGUST 1997

Date of mailing of the international search report

05 SEP 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized official

ERIC F. WINAKUR

Telephone No. (703) 308-3940